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Review / Derleme

Is it time to stage prostate cancer using molecular imaging?

Prostat kanserinde moleküler görüntüleme ile evrelemenin vakti geldi mi?

Özer Güzel[1], Fazlı Polat[2], Ali Atan[2]

1 University of Health and Sciences, Ankara City Training and Research Hospital, Department of Urology, Ankara, Turkey

2 Gazi University, Faculty of Medicine, Department of Urology, Ankara, Turkey

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Yazışma / Correspondence

Ömer Güzel

Üniversiteler Mahallesi 1604. Cad. No: 9

Çankaya, Ankara / Türkiye

E-posta: drozerguzel@gmail.com

Tel: +90 532 430 14 96

ORCID

Ö.G. 0000-0003-4647-4706

F.P. 0000-0002-1219-5082

A.A. 0000-0002-7114-068X

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Özet

Prostat kanseri erkeklerde en sık saptanan kanserlerden birisidir. Tanı koyulduktan sonra tedavi planlaması ve prognozun öngörülebilmesi amacı ile görüntüleme yöntemleri eşliğinde evreleme yapılması gereklidir. Son yıllarda yaşanan teknolojik ilerlemeler ışığında yeni görüntüleme yöntemleri klinik kullanıma girmiştir. Bu amaçla Prostat spesifik membran antijeni (PSMA) pozitron emisyon tomografisi (PET) görüntüleme yöntemi ön plana çıkmıştır. Anatomik ve fonksiyonel görüntüleme sağlaması nedeni ile tümoral (T), nodal (N) ve metastatik (M) açıdan evrelemede birçok avantaja sahiptir. Bu derlemede prostat kanseri evrelemesinde PSMA-PET yönteminin güncel durumu ele alınmıştır.

Anahtar Kelimeler: prostat kanseri, evreleme, pozitron emisyon tomografi

Abstract

Prostate cancer is one of the most common cancers in men. After the diagnosis is made, staging should be undertaken with imaging methods in order to plan the treatment and predict the prognosis. Parallel to technological developments in recent years, new imaging methods have entered into clinical use. Among these methods, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging has come to the fore since it provides anatomical and functional imaging and has many advantages in tumor (T), nodal (N) and metastatic (M) staging. This review discusses the current status of the PSMA-PET method in prostate cancer staging.

Keywords: prostate cancer, staging, positron emission tomography

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancers in men. It is strongly suspected in the detection of abnormal digital rectal examination (DRE) findings and/or increased prostate specific antigen (PSA) levels. The exact diagnosis of PCa is made after the histopathological examination of the tissue obtained by a needle biopsy of the prostate (1). The most common prostate malignancy is prostatic adenocarcinoma.

After the diagnosis of PCa, it is necessary to use clinical data and imaging methods to determine the risk level and stage the disease. Clinical data used to determine the risk level include DRE findings, serum PSA level, and Gleason score obtained during biopsy. Using these data, patients can be classified as low-, medium- and high-risk groups (D'Amico risk classification) (2,3) (Table 1). It is necessary to stage the disease using imaging methods in order to plan the treatment to be applied after diagnosis, perform follow-up after treatment, and predict prognosis. With the technological advances in recent years, new imaging methods have been introduced into clinical use, and it is considered that they will find more place in staging in the near future (4). Multi-parametric magnetic resonance imaging (mpMRI) and positron emission tomography (PET) stand out among new imaging methods that have been adopted in clinical use in recent years.

Recently, PET imaging has become the most investigated method since it provides both anatomical and functional evaluation (5). Prostate-specific membrane antigen (PSMA) is a 750-amino acid transmembrane glycoprotein with folate hydrolase activity expressed by the prostatic epithelium known as N-acetyl-L-aspartyl-L-glutamate peptidase 2 or glutamate-carboxypeptidase. PSMA is a multifunctional enzyme-acting protein capable of activating signaling cascades related to cell nutrition, survival, proliferation, and migration, and the increased expression of this protein in PCa and different malignancies serves as an important theranostic target (6). The theranostic approach is the name given to the combination of a therapeutic agent and a diagnostic method used to define the effect of this agent. It is formed by combining the words therapy and diagnostics/diagnosis. In PET imaging, PSMA is labelled with Gallium-68 (Ga-68) or Fluorine-18 (F-18) radioisotopes to reach the target tissue. Compared to F-18, Ga-68 has many advantages, such as lower positron energy emission and longer half-life, which improves image quality. Therefore, Ga-68 has come to the fore in PET imaging, becoming the most researched method in terms of PCa in recent years. Ga-68 is a Ge-68/Ga-68 generator product with a half-life of 67.63 minutes and a positron emission of 89%. Ga-68-labeled PSMA inhibitor radiosynthesis was first demonstrated by Banerjee et al. at Johns Hopkins University on a preclinical model (7). Later, Eder et al. developed Ga-68 PSMA-11 and showed that this agent specifically entered the cell and maintained its high levels in human prostate cancer cells (8). Since then, other compounds with similar bio-distribution and imaging features, including Ga-68 PSMA-617 and Ga-68 PSMA I&T have also been developed (9). Ga-68 PSMA compounds are all abbreviated as Ga-68 PSMA in international guidelines due to their similarities. In the initial staging of PCa, although there are only limited scientific data, Ga-68 PSMA PET/CT is generally recommended as a new-generation imaging method, since it can provide additional information and potentially contribute to the prediction of possible changes in disease management if conventional imaging is negative or there are suspicious findings (10-12). The latest European Urology Association PCa guidelines state that Ga-68 PSMA PET/CT offers more precise staging than conventional CT and whole body bone scintigraphy in the initial staging of high-risk PCa; however, it is also emphasized that there are not yet sufficient results to prove this. Nevertheless, it is considered that molecular imaging methods will play a larger role in the near future. In this review, the growing role of PET imaging in tumoral (T), nodal (N) and metastatic (M) staging of the disease is summarized.

Role of PSMA-PET/CT in tumor staging

As is known, T staging is generally based on DRE findings. Depending on the practitioner's experience, this subjective method determines the patient's T stage by evaluating parameters such as whether the tumor is palpable, involvement of the lobes, and signs of inva-

Table 1: D'Amico risk classification

Definition			
Low risk	**Medium risk**	**High risk**	
PSA < 10 and GS < 7 (ISUP 1) and cT1-2a	PSA 10-20 or GS 7 (ISUP 2/3) or cT2b	PSA > 20 or GS > 7 (ISUP 4/5) or cT2c	Any PSA value Any GS cT3-4 or cN+
Localized			**Local advanced**

***GS**: Gleason score, **ISUP**: International Society of Urological Pathology, **PSA**: Prostate-specific antigen*

sion (13,14).The contribution of conventional imaging methods to T staging is limited. In parallel with the technological advances in recent years, these limitations have been significantly overcome with mpMRI. The addition of at least two of three methods (diffusion-weighted and contrast-enhanced imaging, and/or apparent diffusion coefficient mapping) to conventional T1 or especially T2-weighted imaging has significantly contributed to the detection of clinically important PCa cases. Although mpMRI has a high negative predictive value, it is clear that there are lesions that cannot be visualized by MRI (15). In a recent prospective study by Lopci E et al., the diagnostic value of Ga-68 PSMA-PET/CT was investigated on 97 patients with suspected PCa, who had negative or positive findings of mpMRI but negative prostate biopsy results. A targeted fusion prostate biopsy was carried out in 64 patients who had PET-positive areas, and clinically significant PCa was detected in 36% (n = 23) of these patients. The authors concluded that Ga-68 PSMA-PET/CT would be sufficient to detect clinically significant PCa in cases where PCa suspicion continues despite a negative initial biopsy (16). In another study in which 21 high-risk PCa cases were evaluated for primary staging, conventional imaging methods and PSMA-PET imaging were compared in terms of their diagnostic accuracy. It was reported that PSMA-PET had a higher diagnostic accuracy than MRI, CT and bone scintigraphy. Although PSMA-PET was not superior to mpMRI in detecting prostatic lesions, it had higher performance in detecting lymph node involvement compared to MRI (95.2% vs 80%). It was also reported to have higher sensitivity than conventional CT in detecting extrapelvic lymph node and bone metastases (100% vs. 75% and 100% vs. 62.5%, respectively) (17). With the development in PET MRI methods and their adaptation to biopsy procedures, they are expected to have higher sensitivity and specificity in detecting PCa in the near future. In addition, studies conducted to evaluate extraprostatic extension before surgery and predict the preference of nerve-sparing surgery and possible biochemical recurrence have reported that PSMA-PET could be a useful imaging method in the assessment of these factors (18).

Role of PSMA-PET/CT in nodal staging

Enlarged lymph nodes dissection provides the most accurate nodal staging. Conventional imaging methods offer only limited information concerning lymph node involvement in preoperative clinical staging. According to calculations performed using the current nomograms of Briganti, Partin and Memorial Sloan Kettering Institute, bilateral enlarged lymph nodes dissection is recommended for patients with a >5% value (19,20). There are many studies concerning the use of the PSMA-PET method for nodal staging. In a study by Maurer et al. including 130 cases in the medium- and high-risk groups, the efficacy of PSMA-PET in detecting nodal involvement before radical surgery was evaluated compared to conventional methods. In that study, it was reported that conventional imaging methods were not sufficient in demonstrating lymph node involvement before radical prostatectomy, while PSMA-PET had higher sensitivity but moderate specificity and reduced the possibility of lower staging of the disease (21). In a meta-analysis conducted by Kim et al., the sensitivity and specificity of PSMA-PET in detecting nodal involvement in medium- and high-risk patients were reported as 71% and 95%, respectively.

Although the authors noted that a more accurate result was achieved in patients with PSMA-PET positivity, they also emphasized that lymph node involvement could not be definitively excluded in those with negative results (22). In another retrospective study evaluating high-risk PCa cases in terms of lymph node involvement, Badaus et al. found the sensitivity and specificity of PSMA-PET to be 33.3% and 100%, respectively. The authors underlined the importance of size in the evaluation of nodal involvement and found the mean size to be 4.3 mm for false-negative metastases and 13.8 mm for node-positive cases (23). In another recent meta-analysis assessing current imaging methods used for lymph node staging, the sensitivity and specificity of diffusion-weighted imaging-MRI in detecting nodal involvement smaller than 1 cm were found to be 41% and 94%, respectively. It was also suggested that PSMA-PET had a higher sensitivity and would soon have a wider area of use in this patient group (24). In another study evaluating the use of Ga-68 PSMA-PET/CT in initial lymph node staging in 51 newly diagnosed high-risk PCa cases, the histopathological correlation analysis revealed that the sensitivity, specificity and accuracy values were 67%, 88%, and 81%, respectively for PSMA-PET and 20%, 99%, and 72%, respectively for conventional imaging (MRI and CT) in a subgroup of patients in which ≥15 lymph nodes were excised (n = 37). The authors stated that Ga-68 PSMA PET/CT was superior to conventional imaging in detecting nodal metastasis, but lymph node dissection remained the gold standard for nodal staging (25). According to these literature data, PSMA-PET/CT seems to have the potential to replace conventional abdominal-pelvic CT in the nodal staging of PCa.

Role of PSMA-PET/CT in M staging

PCa mostly metastasizes to the bone, which is most commonly detected using whole-body bone scintigraphy (26). However, there is an increasing number of studies reporting that PSMA-PET is more efficient in the determination of regional and extra-pelvic metastases compared to conventional imaging methods. (27) In a study involving 129 patients, Schmidt-Hegeman et al. reported that PSMA-PET was superior to CT in detecting distant metastases, and it also assisted in making a decision for adjuvant or salvage radiotherapy when PSA was >0.5 after prostatectomy (28). In recent years, with the widespread use of PSMA-PET, there has been a transition from localized disease and subsequent definitive treatments to systemic treatments. Bone metastases of PCa are mostly blastic-sclerotic; however, they can also be of mixed character, such as lytic-destructive and lytic-blastic. While bone metastases do not yet show reactive-blastic activity in bone tissue, active tumor cells can be detected in the early bone marrow period based onGa-68 PSMA in the presence of molecularly low PSA levels (29, 30). Hofman et al. examined the initial staging of high-risk PCa using Ga-68 PSMA-PET before definitive treatments, such as surgery and radiotherapy. In a multicenter prospective randomized phase III study (proPSMA study) including 302 patients, the authors found that Ga-68 PSMA-PET was superior to conventional methods in detecting lymph node and distant metastases (accuracy: 92% vs. 65%). They also stated that Ga-68 PSMA-PET could specifically detect nodal-visceral and early bone metastases in low-volume disease with high tumor/background activity (activity uptake observed in areas other than physiological distribution is interpreted as pathological). Thus, it was suggested that Ga-68 PSMA-PET assisted in planning an appropriate treatment and revising patient management if necessary, and it had the advantage of involving less radiation exposure compared to traditional methods (19.2 mSv vs. 8.4 mSv). It was also emphasized that there was a need to update current guidelines in light of this information (31). However, criticizing this study, Moore argued that the high cost of PSMA-PET and its low availability in healthcare centers were the most important barriers to the adoption of this method (32). Molecular imaging plays a role not only in staging but also in the treatment management of metastases by targeting PSMA. Targeting PSMA with Lutetium-177, also known as radioligand therapy, has been reported to be effective in the treatment of metastases in patients who have castration-resistant PCa, which is an extremely important development for this patient group (33,34). These findings show that PSMA-PET/CT has significant potential for a theranostic approach not only in the diagnosis phase but also in the treatment phase.

CONCLUSION

It is reported that PSMA-PET is a promising method that can singularly present the data obtained by the combined use of conventional tomographic imaging and whole body bone scintigraphy during the initial detection of PCa. In many recent studies, PSMA-PET/CT has been shown to be more efficient than conventional imaging methods in detecting the presence of intra-prostatic tumors, evaluating nodal involvement, and detecting distant metastases. Although there are no recommendations for the routine use of PSMA-PET in current guidelines, it would not be a far-fetched prediction to state that in the very near future, PSMA-PET will be increasingly adopted for the diagnosis and treatment of PCa and current guidelines will be updated accordingly, as this method becomes more commonly available and more affordable.

Conflict of Interest

All authors declared that there is no conflict of interest.

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Author Contributions

Conception and design; ÖG, AA, Drafting the manuscript; ÖG, Critical revision of the manuscript for scientific and factual content; FP, AA, Supervision; FP, AA.

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