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Korean Journal of Radiology

KJR

Research Highlight: ^{68}Ga-PSMA-11 PET Imaging for Pelvic Nodal Metastasis in Prostate Cancer

Jurgen J. Fütterer, James Nagarajah

All authors: Department of Medical Imaging, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Take-home points

- The sensitivity of ^{68}Ga-prostate-specific membrane antigen (PSMA)-11 PET for detecting pelvic lymph node metastasis is moderate.
- The specificity of ^{68}Ga-PSMA-11 PET in diagnosing pelvic lymph node metastasis is very high.
- A negative ^{68}Ga-PSMA-11 PET cannot preclude lymph node dissection in patients undergoing radical prostatectomy for prostate cancer.
- A positive lymph node on ^{68}Ga-PSMA-11 PET in patients undergoing radical prostatectomy for prostate cancer is highly likely to be a true nodal metastasis.

Pelvic lymph node dissection is an important component in the staging and prognostication of prostate cancer [1]. The current guidelines on prostate cancer from the European Association of Urology, recommend performing extended pelvic lymph node dissection (ePLND) in intermediate- and high-risk patients when the estimated risk for positive lymph nodes exceeds 5% [2]. However, pelvic lymph node dissection is associated with significantly worse intraoperative and perioperative outcomes than no

pelvic lymph node dissection [1]. Morphological imaging techniques, such as computer tomography or magnetic resonance imaging (MRI), are not accurate enough to allow for the omission of ePLND. Therefore, noninvasive molecular imaging may play a role in the detection of pelvic lymph node metastases.

Recently, Hope et al. [3] reported the diagnostic accuracy of positron emission tomographic (PET) imaging for PSMA ^{68}Ga-PSMA-11, towards the detection of pelvic nodal metastases. In this multicenter (two centers) open-label single-arm phase 3 imaging trial, ^{68}Ga-PSMA-11 PET was compared with histopathology at the time of radical prostatectomy and pelvic lymph node dissection. They found that in male with intermediate-and high-risk prostate cancer, the sensitivity and specificity of ^{68}Ga-PSMA-11 PET were 40% and 95%, respectively, and the positive and negative predictive values were 75% and 81%, respectively, for detecting pelvic nodal metastases. This study included 764 male with intermediate- or high-risk prostate cancer who underwent ^{68}Ga-PSMA-11 PET imaging. Of these, 277 patients underwent radical prostatectomy and developed the primary efficacy population. All imaging studies in this population were read by three independent blinded central readers who were not involved in the study design or data acquisition. Images were interpreted visually using Prostate Cancer Molecular Imaging Standardization Evaluation criteria. Based on the pathology reports, 75 of 277 patients (27%) had pelvic nodal metastases.

Interestingly, when 10 patients with false-positive results were retrospectively reviewed, five of these 10 patients had a persistent elevation of serum prostate-specific antigen after radical prostatectomy, and a post-surgery ^{68}Ga-PSMA-11 PET scan showed the same PET-positive lymph nodes as the pre-surgery scan. Most likely, these lymph

nodes were not removed, and the suboptimal reference standard might have decreased specificity. Moreover, there may be a selection bias of the patients with available histopathology, since a significant number of patients did not undergo surgery after ^{68}Ga-PSMA-11 PET, likely due to the non-curative disease setting, of which 52% showed an N1 status on PET.

In the preoperative setting, the reported sensitivity was in line with other comparable studies (38%–42%) [4,5]. Interestingly, the sensitivity and positive predictive value of ^{68}Ga-PSMA-11 PET were higher in patients with biochemical recurrence after surgery or radiotherapy. In clinical practice, when a negative ^{68}Ga-PSMA-11 PET is used as the basis for not performing pelvic lymph node dissection, 80% of male would avoid unnecessary pelvic lymph node dissection and subsequent side effects. However, due to the limited sensitivity of this technique, 20% of patients who undergo radical prostatectomy alone will have unresected positive nodes.

Other imaging techniques, such as intraoperative PSMA-guided or fluorescence guided techniques, may improve the ^{68}Ga-PSMA-11 PET sensitivity in intermediate- and high-risk prostate cancer populations. Dual-labeling strategies that allow both acoustic and visual detection of PSMA-expressing tumor lesions are promising developments [6]. Unfortunately, these are not available in clinical practice. However, owing to technical limitations, micrometastases remain challenging even with these new techniques.

In summary, the reported negative predictive value indicates that 20% of the patients who underwent radical prostatectomy and lymph node dissection had positive nodes at pathology despite concurrent negative findings on ^{68}Ga-PSMA-11 PET. This may imply that a negative ^{68}Ga-PSMA-11 PET result cannot preclude lymph node dissection in this patient group. However, a positive lymph node on ^{68}Ga-PSMA-11 PET is highly likely (specificity 95%) to be a true lymph node metastasis, and thus would guide corresponding patient management.

Key words
Prostate cancer; Prostate-specific membrane antigen; Positron emission tomography

Availability of Data and Material
Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest
Jurgen J. Fütterer who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

ORCID iDs
Jurgen J. Fütterer
   https://orcid.org/0000-0001-6800-2879
James Nagarajah
   https://orcid.org/0000-0002-3555-0809

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