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Letter to editor

^{68}Ga-Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography: How Much Specific It Is?

Dear Editor,

I went through the Review article, "^{68}Ga-prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) for prostate cancer imaging: A narrative literature review" by Oliveira *et al*.[1] The manuscript is well written and well appreciated as it covers a narrow review on ^{68}Ga-PSMA PET/CT which has become a popular choice in the management of prostate cancer.

As there is increase in concern and ongoing trials of therapy-related with positive findings on the metastatic work up in ^{68}Ga-PSMA PET/CT, it is very much essential and ethical while interpreting the prostate-specific membrane antigen (PSMA) uptake. For this reason, I felt this review should also pay little attention regarding the false-positive uptakes of PSMA whose number is increasing gradually as more and more the modality is being explored.

Chang *et al*. demonstrated the strong reaction of five anti-PSMA antibodies including 7E11 in the in the neovasculature of wide variety of malignant neoplasms including renal cell carcinoma (RCC), transitional cell carcinoma, testicular embryonal carcinoma, colonic adenocarcinoma, neuroendocrine carcinomas, glioblastoma multiforme, malignant melanoma, pancreatic duct carcinoma, nonsmall cell lung carcinoma, soft tissue sarcomas, and breast carcinoma. Even though prostatic adenocarcinoma tumor cells showed PSMA positivity in all cases in the study, neovasculature of prostatic adenocarcinoma showed PSMA positivity only in 2 of 12 cases.[2]

Apparently, the tumor neoangiogenesis is the mechanism attributed to increased Ga-PSMA uptake in the tumor sites in nonprostatic malignancies. Recently, ^{68}Ga-PSMA uptake has been demonstrated in multiple myeloma. In addition, PSMA uptake has been described in papillary carcinoma of thyroid, gastrointestinal stromal tumor.[3]

Synchronous metastatic inguinal, pelvic, and retroperitoneal lymph node metastases have been proved showing PSMA uptake in case of penile and prostate cancer. PSMA expression was seen in tumor vessels and may explain the ^{68}Ga-PSMA-PET/CT positivity of inguinal nodes involved in squamous cell carcinoma.[4] In addition, in another reported case, retroperitoneal lymph node and thyroid tissues showed metastases from RCC, whereas the pelvic lymph node exhibited metastasis from prostate cancer in ^{68}Ga-PSMA PET/CT.

As ^{68}Ga-PSMA PET/CT has become a popular gateway for theranostic with Lu-PSMA, it becomes very much essential to understand the pattern and pathophysiology of benign uptakes of PSMA as it can wrongly categorize benign nodes to be of metastatic node which may end up in wrong upstaging tumor burden assessment, thus putting unnecessary radiation burden on the patient apart from all other socioeconomic burden.

In 2 cases of Ga-PSMA PET/CT in prostate cancer patients, symmetrical bilateral involvement of mediastinal and hilar lymph nodes showed biopsy-proven sarcoidosis.[5] Subacute cortical cerebral infarct, follicular thyroid adenoma, and benign senile seminal vesicle amyloidosis in a prostate cancer patient showing focal uptake on PSMA PET/CT have also been reported. Furthermore, in another case, a 65-year-old male with left-sided pelvic pain on evaluation was found to have histopathologically proven Paget's disease of pelvis showing increased PSMA uptake.[6]

Even though imaging using Anti-PSMA agents tagged with radionuclides are considered tumor specific, these reports warrant caution in reporting lesions showing increased uptake as metastases in patients with prostatic adenocarcinoma. Pathological confirmation of suspected lesions or ^{18}fluid fluorodeoxyglucose PET/CT should be done to rule out synchronous or metachronous malignancy which can show similar uptake to avoid mismanagement in such patients. Although it is a potential drawback of the modality, at the same time, it also gives a scope for innovation of theranostic for many nonprostatic cancers, and further trials should be encouraged like in multiple myeloma and thyroid cancer.

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As the lists of benign uptakes are also in the rise, there should be high degree of suspicion and pathological confirmation in isolated pelvic/retroperitoneal lymph nodes or seminal vesicle uptake so that they should not be over treated with Lu-PSMA without undergoing histological confirmation. Further studies including larger trials can only validate its specificity in prostate cancer or else it may be a tool to guide sites for pathological confirmation.

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Conflicts of interest
There are no conflicts of interest.

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