An overview on prostate-specific membrane antigen uptake in malignancies other than prostate cancer: A pictorial essay

ABSTRACT
Prostate-specific membrane antigen (PSMA) is a Type II transmembrane glycoprotein which is extremely overexpressed in prostate cancer epithelial cells. Recently, PSMA-targeted small molecule labeled with $^{68}$Ga and $^{99m}$Tc allowed precise molecular imaging of prostate cancer and PSMA-targeted small molecule labeled with $^{177}$Lu leads to the development of radionuclide-targeted therapy of prostate cancer. Despite its name, it has been shown that PSMA has been expressed in several malignancies which can be due to significant neovascularization. Present pictorial assay reports the nonspecific tracer uptake in some malignancies during $^{68}$Ga-PSMA positron-emission tomography/computed tomography imaging and $^{99m}$Tc-PSMA scintigraphy.

Keywords: $^{68}$Ga-prostate-specific membrane antigen positron-emission tomography/computed tomography, $^{99m}$Tc-prostate-specific membrane antigen scintigraphy, prostate cancer, prostate-specific membrane antigen and nonspecific uptake

INTRODUCTION
Prostate-specific membrane antigen (PSMA) is a Type II transmembrane glycoprotein which is extremely overexpressed in prostate cancer epithelial cells.[1] Higher tumor stage and grade, tumor dedifferentiation, hormone resistance, and metastatic disease lead to increase in overexpression of PSMA.[2] Although PSMA first was identified in the prostate gland, its expression in the duodenal epithelium, proximal tubule cells in the kidney, salivary glands, and tumor-associated vascular endothelium have been revealed in eventual histopathological studies.[3-5]

Recently, innovative development of PSMA-targeted small molecule labeled with $^{68}$Ga and $^{99m}$Tc allowed precise molecular imaging of prostate cancer and PSMA-targeted small molecule labeled with $^{177}$Lu led to the development of radionuclide-targeted therapy of prostate cancer.

$^{68}$Ga-PSMA positron-emission tomography (PET) since its first use in 2013 has revolutionized the management and imaging of patients with prostate cancer. Numerous studies have proved the high efficacy of $^{68}$Ga-PSMA in diagnosing, staging, follow-up, restaging, and evaluating treatment response.[6-9]

Regarding the cost benefits and broader availability of single-photon emission computed tomography (CT)
compared to PET, ⁹⁹mTc-labeled small molecule inhibitor has been developed. The clinical evaluation and detection rate of ⁹⁹mTc-PSMA in staging, recurrence, and treatment response of patients with prostate cancer have been evaluated in previous studies.⁹⁻¹³ Schmidkonz et al.⁹ used ⁹⁹mTc-MIP-1404 as a ⁹⁹mTc-labeled PSMA inhibitor for the detection of prostate cancer with biochemical recurrence. Tracer-positive lesions were detected in 77% of patients, which indicated that this radiotracer has a high probability in the management of prostate cancer patients with biochemical recurrence. In another study, Reinfelder et al.¹⁴ evaluated the detection efficacy of ⁹⁹mTc-MIP-1404 in prostate cancer patients with biochemical recurrence. It has been reported that 70% of patients showed positive lesion which revealed that MIP-1404 is a promising radiotracer for the detection of prostate cancer lesions. However, despite its name, in addition to prostate tissue, PSMA is physiologically expressed in a multiple number of nonprostatic malignancies because of PSMA mRNA transcripts and protein expression in the endothelium of tumor-related neovasculature, leading to potential pitfalls in the clinical use of PSMA-targeted imaging.⁴⁻⁹,¹³ Nevertheless, PSMA expression in nonprostatic malignancies may prove beneficial in therapeutic and imaging targets for these conditions. Table 1 represents malignancies other than prostate cancer which shows PSMA uptake in previous researches. In this pictorial assay, we reported a few nonprostatic malignancies cases, i.e., differentiated thyroid cancer, esophageal cancer, pancreaticobiliary adenocarcinoma, ureteral cancer, cholangiocarcinoma, pancreatoblastoma, hepatoblastoma, and carcinoma of unknown primary showing PSMA expression during ⁹⁹mTc/¹⁷⁷Lu-PSMA scintigraphy and ⁶⁸Ga-PSMA PET imaging [Figures 1-8].

CONCLUSION

Regarding the current literature, interpretation and reporting the PSMA scan in prostate cancer needs careful evaluation as its specificity is limited by some false-positive findings. These limitations may increase the diagnostic pitfalls and decrease the confidence of interpreting physicians. Nonspecific uptakes of ⁶⁸Ga-labeled PSMA PET/CT and ⁹⁹mTc/¹⁷⁷Lu-PSMA scintigraphy for prostate imaging at the other malignancies

Table 1: Previous literatures on prostate-specific membrane antigen uptake in malignancies other than prostate cancer

| Authors          | Diagnosis                                      |
|------------------|------------------------------------------------|
| Taywade et al.⁴³ | Thyroid cancer                                 |
| Verma et al.⁴¹   | Oral cancer                                    |
| Bychkov et al.⁴⁸ | Gastric and colorectal cancers                 |
| Sollini et al.⁴⁸ | Lung cancer                                    |
| Haffner et al.⁴⁶ | Breast cancer                                  |
| Haffner et al.⁴⁶ | Endometrial and ovarian cancer                  |
| Wang et al.⁵⁰    | Renal cancer                                   |
| Wernicke et al.⁴⁸| Bladder cancer                                 |
| Wernicke et al.⁴⁸| Glioblastoma                                   |
| Baccala et al.⁴⁸ | Follicular lymphoma                            |
| Rhe et al.⁴⁸     | Brain tumors                                   |
| Samplaski et al.⁴⁷| Multiple myeloma                               |
| Nomura et al.⁴⁸  | Hepatocellular carcinoma                       |
| Wernicke et al.⁴⁸| Osteosarcoma                                   |
| Kanthan et al.⁴⁷ | Hepatocellular cholangiocarcinoma               |
| Sasikumar et al.⁴⁹| Melanoma                                      |
| Sasikumar et al.⁴⁹| Thymoma type B2                                |
| Sasikumar et al.⁴⁹| GE junction adenocarcinoma                     |
| Sasikumar et al.⁴⁹| Signet-ring cell carcinoma                     |
| Alipour et al.⁴⁷ | GI stromal tumor                               |
| Anconina et al.⁴⁷| Rectal adenocarcinoma                          |
| Krahmajar et al.⁴⁷| Pancreatic neuroendocrine tumor                 |
| Malik et al.⁴⁹   | Adrenocortical carcinoma                       |
| Malik et al.⁴⁹   | Squamous cell carcinoma of the penis            |

Figure 1: A 54-year-old woman with differentiated thyroid cancer underwent ablation with radiiodine therapy. Posttreatment scan revealed just extensive uptake of I-131 in thyroid bed and did not show any remarkable uptake in the rest of the body. As the previous study indicated the Prostate-specific membrane antigen expression in differentiated thyroid cancer,¹⁸,²⁰ ⁹⁹mTc-PSMA-specific membrane antigen scintigraphy was done for disease assessment showing diffuse severe uptake in the lung (a). As mentioned in previous studies,⁴⁵⁻⁵⁰ currently, the therapeutic options are limited for patients with metastasized, ¹³¹I-resistant differentiated thyroid cancer, therefore, in another case, ⁹⁹mTc-PSMA-specific membrane antigen scintigraphy was performed in a 40-year-old male with radiiodine refractory differentiated thyroid cancer. The scan showed a diffuse severe uptake of radiotracer in the lung (b). Therefore, such patients can be a candidate for novel therapy with ¹⁷⁷Lu-prostate-specific membrane antigen.
Figure 2: $^{68}$Ga-prostate-specific membrane antigen positron emission tomography/computed tomography was performed for a 71-year-old male with a history of prostate adenocarcinoma (GS: 4 + 5) underwent prostatectomy 6 years ago. One year after prostatectomy, due to local recurrence, the patient underwent second surgery, external beam radiation therapy and brachytherapy. Due to rising prostate-specific antigen, $^{68}$Ga-prostate-specific membrane antigen positron-emission tomography/computed tomography was performed for recurrence evaluation. The scan revealed a mid-esophageal mass with esophageal stenosis and highly increased radiotracer uptake, suggesting a second primary cancer with mediastinal lymph nodes metastases. According to the prior studies, increased prostate-specific membrane antigen expression maybe due to significant neovascularization revealed in gastroesophageal cancers[21,31].

Figure 3: $^{68}$Ga-prostate-specific membrane antigen positron emission tomography/computed tomography was performed for a 46-year-old woman with a history of multiple hepatic lesions which on biopsy it was adenocarcinoma most likely pancreatobiliary underwent 7 courses of chemotherapy. The scan revealed a 54 mm × 39 mm mass lesion in the segment 5 liver with a maximum standardized uptake value of 11.32 corresponding to the recently computed tomography and fluorodeoxyglucose-positron emission tomography/computed tomography finding. The fluorodeoxyglucose-positron emission tomography/computed tomography, also, showed a solitary hepatic lesion in the right hepatic lobe with the mean standardized uptake value of 2.54.

Figure 4: $^{68}$Ga-prostate-specific membrane antigen positron emission tomography/computed tomography was performed for a 53-year-old male with high-grade transitional cell carcinoma of the ureter received chemotherapy. The patient presented with abdominal pain, bowel obstruction, and colostomy bag. The scan revealed prostate-specific membrane antigen uptake in peritoneal implants.

apart from prostate cancer are being reported. Case reports have shown PSMA avidity in high-grade gliomas, lung cancer, breast cancer, multiple myeloma, and malignant melanoma.
due to the PSMA expression in the endothelial cells of the tumor neovasculature. The finding of PSMA expression in these malignancies may lead to radioligand-based therapeutic options.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.
High expression of prostate-specific membrane antigen in pelvic bones, and both femurs osseous metastasis in the thoracic and lumbar spine, some ribs, bilateral prostate-specific antigen level (0.83 ng/ml) and immunohistochemistry excluded according to the prostate magnetic resonance imaging, serum

Figure

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