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# Incidental discovery of gastrointestinal stromal tumor via PSMA-PET/CT imaging: Insights from a case report

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ABSTRACT

PSMA-PET/CT has emerged as a superior diagnostic tool for prostate cancer, demonstrating enhanced accuracy over conventional imaging methods. Although sensitive for detecting local and metastatic prostate tumors, it can also identify other non-prostate PSMA positive lesions. Here, we report a rare case of a 67-year-old patient with metastatic prostate adenocarcinoma who was found to have an incidental Gastrointestinal Stromal Tumor (GIST), during restaging with 68Ga-PSMA-11 PET/CT. Given the broad application of PSMA PET/CT in prostate cancer, its role in diagnosing other non-prostate PSMA tumors remains uncertain, highlighting the need for further research into its application in cancer management.

## 1. Introduction

Prostate Specific Membrane Antigen (PSMA)-ligand PET/CT has increasingly been employed as a staging tool for prostate cancer following FDA-approval in 2020. Studies have demonstrated its superiority in diagnosing both local and metastatic disease compared to conventional imaging methods such as CT and bone scans. Its effectiveness as diagnostic tool is attributed to the binding of a targeted radioligand to the highly expressed PSMA protein in prostate cancer cells.[1] However, PSMA expression is not specific to prostate cancer, as it is also present in the cell membrane of both normal and other malignant tissues.[2] Since the adoption of PSMA PET/CT scan in clinical practice, incidental findings of non-prostate tumors have been increasingly reported.[3,4] Here, we present a rare case of a Gastrointestinal Stromal Tumor (GIST) detected using a restaging PSMA PET/CT scan in a patient with metastatic prostate adenocarcinoma.

## 2. Case presentation

A 67-year-old patient underwent radical prostatectomy after being diagnosed with Gleason score 4 + 3 prostate adenocarcinoma in 2016. PSA was undetectable post-operatively until a biochemical recurrence was noted in 2019. Following adjuvant pelvic radiation, a gradual rise in PSA was observed over the next year, at which point the patient underwent a fluciclovine F18- PET/CT scan. No evidence of metastatic disease was shown, but PSA continued to increase and the patient began intermittent Androgen Deprivation Therapy (ADT) in 2021.[5]

In 2022, with PSA elevated to 2.4 ng/ml, restaging CT and bone scans revealed metastatic lesions in the skull, clavicle and spine, along with an intraluminal polypoid filling defect in the greater curvature of the stomach, suggestive of either polyp or GIST. F18-FDG piflufolastat PET/CT confirmed the metastatic lesions but showed no avidity in the stomach. No endoscopy was performed at this time.

Following stereotactic radiotherapy to the avid PSMA lesions, the PSA nadired to undetectable levels. However, a follow-up 68Ga-PSMA-11 PET/CT one year later, in response to a slow PSA rise to 3.22 ng/ml, demonstrated a new avid lesion at the right humeral head. Additionally, focal radiotracer uptake was noted at the left lateral greater curvature of the stomach (SUVmax = 3.4) (Fig. 1), prompting further evaluation with endoscopy.

An upper endoscopic ultrasound was performed, identifying a 15mm*13mm hypoechoic subepithelial lesion in the greater curvature and the posterior wall of the gastric body. Biopsy confirmed a CD34$^{+}$, CD177+, S100 (−) lesion with a Ki-67 index of approximately 1 %, consistent with a diagnosis of Gastrointestinal Stromal Tumor (GIST).

The patient completed radiotherapy for the new metastatic prostate lesion and continued intermittent hormonal therapy. His most recent PSMA PET/CT restaging revealed several areas of low-level avidity in addition to the gastric tumor, and he is currently managed with systemic therapy for his prostate cancer. The GIST is being followed conservatively without active intervention.

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## 3. Discussion

PSMA PET/CT is a specific imaging technique used for staging prostate cancer, by detecting PSMA molecule, a type II- transmembrane protein prevalent in local and metastatic prostate cancer tissues. However, PSMA is also found in several normal tissues including the prostate, testis, ovary, endometrium, kidney, liver, small intestine, spleen and the brain.[6] Besides being highly expressed in prostate adenocarcinoma, PSMA is often elevated in tumor epithelial and neovascular endothelial cells of other solid tumors.[7] This broad expression pattern can explain why non-prostatic tumors have been identified using PSMA-ligand specific imaging techniques, including clear cell carcinoma, melanoma, urothelial carcinoma, lung and pancreatic neuroendocrine tumors, lung, gastric and colon adenocarcinomas.[1,8]

PSMA acts by catalyzing the hydrolysis of C-terminal glutamate residues. It functions as a folate hydrolase when polyglutamylated folate serves as the enzyme's substrate, releasing folic acid and glutamate. High levels of folic acid are essential for proliferating cancer cells as they mediate key metabolic processes including DNA synthesis, protein methylation, amino-acid metabolism and methionine production for polyamine synthesis, the latter being notably elevated in prostate cancer.[9,10] Glutamate, in turn, activates the upregulated metabotropic glutamate receptors (mGluRs), promoting tumor growth via the signaling Akt-mTOR pathway.[11]

Similarly, PSMA's folate hydrolase activity in the neo-vasculature of most solid tumors promotes endothelial cell invasion through γ1-integrin activation, while folate and glutamate formation stimulate angiogenesis through increased nitric oxide (NO) production.[12]

Another source of glutamate results from PSMA's activity as a N-acetylated alpha-linked acidic dipeptidase (NAALADase) where it converts N-acetylaspartylglutamate (NAAG) into glutamate and N-acetylaspartate (NAA). While PSMA's NAALADase activity has been mainly studied in the mammalian nervous system, recent evidence also suggests a significant role in cancer. NAAG may serve as a glutamate reservoir for PSMA-expressing cells, especially when other glutamate sources are limited.[13] Glutamate acts both as a signaling molecule and a metabolic mediator in several pathways, including de novo purine synthesis, amino acid and glutathione biosynthesis and lipogenesis. Both elevated NAAG and glutamate levels are associated with tumor aggressiveness and growth.[14,15]

In this case report, we document the detection of a GIST tumor with 68-Ga-PSMA-11 PET/CT scan during restaging of a patient with metastatic prostate adenocarcinoma. This case adds to the existing literature on the detection of non-prostate tumors and the limited reports of GIST tumors in the stomach using this imaging tool.[16–19]

GISTs are the most common mesenchymal-origin tumors in the gastrointestinal tract, originating from interstitial cells of Cajal. Though rare, around 20 % of GIST patients present with an additional malignancy before or after the GIST diagnosis, with prostate cancer being the most frequent co-diagnosis.[20] Notably, PSMA, which is normally expressed in gastrointestinal ganglia, is also found in GIST tumors.[16–19] Prostate cancer's dependency on glutamate raises questions about the impact of incidental PSMA-positive non-prostate tumors, which could potentially serve as secondary glutamate sources. This possible connection warrants further exploration to understand the metabolic and clinical significance of PSMA expression beyond prostate cancer.

While most GISTs can be detected with FDG-based imaging, some cases may show differences between FDG and 68-Ga-PSMA imaging techniques.[18] In our case, the stomach tumor was not avid on the F18-FDG piflufolastat PET/CT scan but was detected on the 68-Ga-PSMA-11 PET/CT during the patient's restaging. Whether the tumor did not express PSMA initially or if the F18-FDG piflufolastat PET/CT scan was unable to detect it remains unclear.

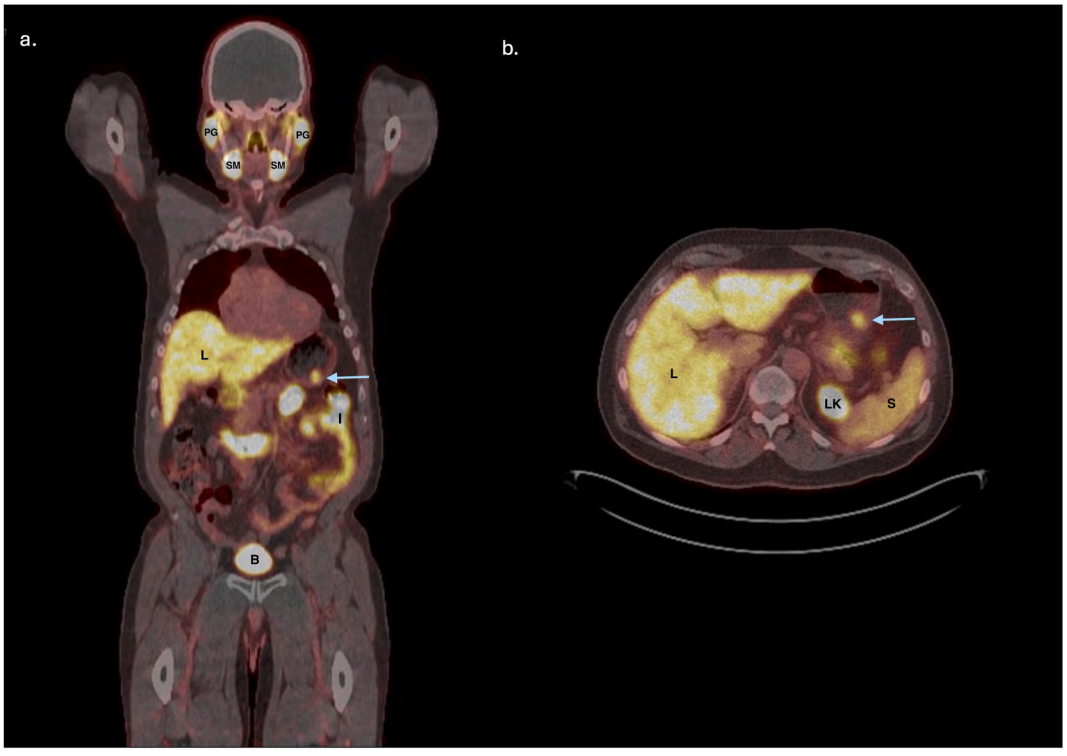


**Fig. 1.** Ga-68 PSMA-PET/CT imaging (a) Coronal section showing a focal radiotracer uptake (Blue arrow) at the left lateral greater curvature of the stomach (SUV: 3–173). (b) Axial view of the same lesion. Physiologic PSMA uptake in the parotid/salivary glands, liver, spleen, intestine, kidney and bladder. PG = Parotid gland; SM = Submandibular gland; L = Liver; S = Spleen; I = Intestine; B = Bladder; LK = Left Kidney.(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

## 4. Conclusion

In conclusion, PSMA-PET/CT not only enhances the staging of prostate cancer but also has the potential to reveal incidental PSMA positive non-prostate tumors that might otherwise go undetected. However, the broader diagnostic value of PSMA PET/CT and the clinical significance of PSMA expression in these non-prostate tumors remain uncertain, emphasizing the need for further investigation into its role in cancer management.

## CRediT authorship contribution statement

**Venetia A. Florou:** Writing – review & editing, Writing – original draft, Investigation. **Diane K. Reyes:** Writing – review & editing, Resources, Data curation. **Kenneth J. Pienta:** Writing – review & editing, Supervision, Conceptualization.

## Ethics statement

Written informed consent was obtained from the patient to publish any potentially identifiable images or data in this article.

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## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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