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A case report of prostate specific membrane antigen positron emission tomography and risk of overtreatment in a man on active surveillance for early-stage prostate cancer

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Abstract

We report the case of a 63 years-old man managed with active surveillance for low-risk prostate cancer for seven years, who underwent radical prostatectomy due to multiple uptakes at prostate specific membrane antigen positron emission tomography ordered due to rising PSA despite three negative surveillance biopsies and three negative multiparametric magnetic resonance imaging scans. The final pathology specimen showed organ confined, low volume grade group 1 disease (Gleason 3+3), without lymph node involvement and with clean surgical margins. The patient has been biochemical recurrence free for three years post prostatectomy.

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Introduction

The clinical utility of Prostate-Specific Membrane Antigen Positron Emission Tomography (PSMA PET) in tailoring decision making of men on Active Surveillance (AS) for early-stage Prostate Cancer (PCa) is unknown [1]. Few studies evaluated its application in this setting, showing conflicting results [2,3]. Moreover, there is evidence that malignant and benign neoplasms other than PCa may determine false positive findings at PSMA PET [4]. The Hospital Pope John XXIII (HPG) AS program relies on sequential biopsies and Magnetic Resonance Imaging (MRIs) to evaluate disease progression, according to the European Prostate Cancer Research Active Surveillance (PRIAS) protocol, dedicated radiologists and pathologists routinely report biopsies and review MRIs [5]. Fluorine 18 (^{18}F) or ^{68}Ga-PSMA PET is adopted as imaging modality for men with biochemical recurrence after curative-intent treatment, and in men with newly diagnosed high-risk PCa. Here we present the case of a man initially followed on AS, who underwent sequential MRIs and biopsies due to a persistently increasing PSA, and eventually underwent Radical Prostatectomy (RP) after a PSMA PET showed multiple nodal involvement.

Case presentation

The patient presented in 2014, at age 63, with Gleason 3+3, Grade Group (GG) 1 PCa involving 5% of a single core, from the intermediate portion of the right lobe, in a 16-core transrectal biopsy performed at an outside institution. He underwent repeated 18-core transrectal confirmatory biopsy, reviewed by the attending uropathologist at HPG, showing no evidence of cancer. He was therefore confirmed on AS with low-risk PCa, nonsuspicious Digital Rectal Examination (DRE), PSA 6.7 ng/mL, prostate volume 90cc, and PSA density 0.07 ng/mL/cc. The only chief complaints were bothersome lower urinary tract symptoms, which improved after the introduction of an oral alpha-blocker. One year later, he underwent his first MRI due to rising PSA (10.1 ng/mL), which showed a highly suspicious 17mm left base/transitional lesion, scored 5 according to the Prostate Cancer Imaging Reporting and Data System version 2 (PI-RADS). The subsequent MRI targeted (5 cores) and systematic (15 cores) biopsy showed only atypical small acinar proliferation in the same systematic area where GG 1 was initially diagnosed two years earlier. As shown in Table 1, the patient underwent two further MRIs and biopsies without evidence of PCa, and persistent negative scans (PI-RADS 1). At first repeated MRI, the previously suspicious lesion was re-reviewed as likely an ectopic benign prostatic hyperplasia nodule. Seven years after diagnosis, a new follow up MRI was nonsuspicious in terms of prostatic lesions, but evidenced suspicious enlarged nodes (Figure 1). After a multidisciplinary discussion, a ^{18}F-PSMA PET was ordered due to continuously rising PSA (22.1 ng/mL), showing high uptake in the anterior portion of the prostate, uptake on the right external, and left common iliac lymphnodes (Figure 2). The patient underwent a further biopsy, without evidence of cancer. After re-reviewing all clinical and radiological findings, the treating physician, after shared decision making with the patient, opted for RP with super extended pelvic lymphnode dissection. The final pathology report was as follows: 140g prostate, GG 1 involving <5% of the right lobe, pT2, pN0, R0, with 32 lymph nodes removed (Figure 3). The patient is biochemical recurrence free to the date this manuscript was submitted for publication.

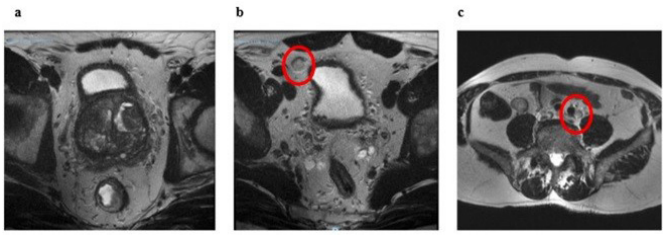

Figure 1: Latest (7 yrs) multiparametric MRI showing PI-RADS 1, **(A)** but suspicious right external iliac node **(B)** and left common iliac node **(C)**.

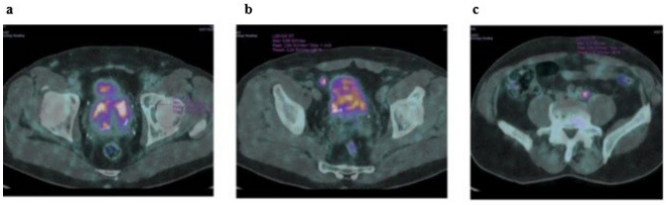

Figure 2: Prostate specific membrane antigen PET showing left anterior prostatic uptake **(A)**, multiple nodal uptakes **(B-C)**.

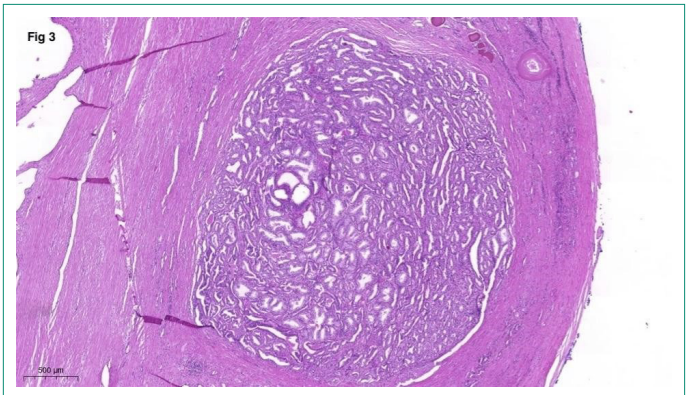

Figure 3: Radical prostatectomy pathology slides showing organ confined grade group 1 disease.

Table 1: Sequential evaluations of the case during follow-up.

Characteristic	Baseline	One year	Two years	Four years	Seven Years
PSA (ng/mL)	7.2	6.7	10.1	15.2	22.1
PSAd (ng/mL/cc)	0.08	0.07	0.11	0.13	0.15
Volume (cc)	90 (TRUS)	90 (TRUS)	90 (MRI)	120 (MRI)	150 (MRI)
MRI	-	-	PI-RADS 5	PI-RADS 1	PI-RADS 1
Biopsy	GG 1	Negative	ASAP	Negative	Negative
DRE	T1c	T1c	T1c	T1c	T1c

Abbreviations: PSA: Prostate Specific Antigen: PSAd: Prostate Specific Antigen Density; TRUS: Transrectal Ultrasounds; MRI: Magnetic Resonance Imaging; PI-RADS: Prostate Imaging Reporting and Data System; ASAP: Atypical Small Acinar Proliferation.

Discussion

The goal of AS is to avoid or postpone treatment for patients with indolent PCa that will likely not determine long-term morbidity and mortality [1]. The introduction of novel imaging modalities demonstrated a benefit in risk stratification for patients with newly diagnosed high-risk PCa [6]. However, its application in the setting of low-risk PCa managed with AS is controversial [2]. Heetman et al demonstrated that the use of Gallium-68 (^{68}Ga) PSMA PET early during AS yields to a significant number of patients found with higher-grade cancer due to additional biopsies performed for local positive molecular imaging [3]. Interestingly, they also reported a case of a patient operated due to a positive nodal spot and found without lymphnode metastases and GG 1 at final pathology. Both cases represent an example of overtreatment driven by novel imaging modalities not validated in the setting in which they were adopted.

Prostatic false positive findings where benign hyperplasia and foci of prostatitis may mimic pathologic uptake are well known [7]. Conversely, PSMA PET has remarkable specificity for nodal lesions, even though fibrosis or inflammatory changes may cause false positive results. It could be argued that involved lymphnodes might be missed during lymphnode dissection, however, the patient is free of biochemical recurrence three years after radical prostatectomy. It should be emphasized that PSMA-avid benign lesions are almost five times more likely for ^{18}F-PSMA PET in comparison to ^{68}Ga-PSMA PET [8] Specifically, ^{18}F-PSMA PET is associated with the highest detection rate of non-specific bone lesions. These lesions are common and demonstrate increased uptake on PET but have no correlate on conventional imaging with computed tomography or MRI [9].

Isolated case reports do not justify recommendations for daily clinical practice. However, it is biologically plausible that a scan suspicious for distant metastases in a man with multiple sequential negative biopsies might be falsely positive, especially in a clinical setting where the incidence of metastases and disease-specific mortality is close to zero [10]. On the other hand, his persistently high PSA, in the absence of a clear history of chronic prostatitis, was the main driver of decision making. Patient's anxiety and request for reassurance can further lead clinicians to seek alternative diagnostic strategies, which can lead to misleading results.

Finally, it is worth considering that in a hypothetical setting where GG 1 would not be called cancer, this gentleman would probably undergo the same clinical pathway, but the negative biopsy after the PSMA PET scan would have led to continuation of monitoring rather than surgery.

Conclusion

Despite this being the second reported case of overtreatment due to a positive novel molecular imaging technique, clinicians should be cautious when using PSMA PET during AS, since false positives will expose patients to the harms of overtreatment if aggressive disease is not histologically confirmed. Further research should address the correct use of molecular imaging techniques in the AS setting.

Consent: Written informed consent was obtained from the patient.

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