Prostate cancer clinical presentation and differentiation from prostatitis: a brief radiological overview

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Abstract

Correctly diagnosing prostatitis or prostate cancer can be particularly difficult even for the most experienced clinician, especially in the case of recurrent prostate cancer. Prostate-specific antigen (PSA), which is not typically ordered in the initial assessment of prostatitis, lacks specificity and is mostly used as a general screening tool. However, there are multiple imaging techniques in the radiologist's armamentarium that can aid in differentiating the two conditions. This review article aims to outline the current diagnostic guidelines for prostatitis and prostate cancer, highlight the imaging features which differentiate the two conditions, and perform a cost-benefit analysis of using advanced imaging techniques in prostate cancer screening.

Keywords: prostatitis, prostate cancer, PSMA PET, MRI, PI-RADS

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Introduction

Prostatitis is inflammation of the prostate gland possibly through infection though in many cases the exact etiology is unknown. When caused by an infection, coliform pathogens such as *Escherichia coli* may enter through the urethra via the intraprostatic reflux. Prostatitis is generally divided into four types. Type 1, also known as acute bacterial prostatitis, is usually caused by ascending urinary tract infection (UTI) or after transrectal prostate biopsy.[1] Those with recurrent UTIs or persistent infection lasting more than three months may fall under chronic bacterial prostatitis or type 2. Chronic prostatitis/chronic pelvic pain syndrome, type 3 or prostatodynia, may be caused by reflux of urine within the prostate among other causes. It is also the most common type of prostatitis. Those diagnosed with type 3 prostatitis require the physician to utilize the UPOINT approach to individualize treatment. It stands for the following six domains: urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic, and tenderness of the muscles.[2] Discussion about the UPOINT approach is beyond the scope of this paper. Lastly, asymptomatic inflammatory prostatitis or type 4 is largely found incidentally through undergoing evaluation for other indications such as seminal analysis for infertility or on prostate biopsy.[3]

Chronic bacterial prostatitis affects mainly young and older-aged men in a bimodal distribution pattern.[4] Individuals with diabetes, smoking history, or previous urinary tract procedures/instrumentation are at an increased risk. Specifically, men with anatomical structural abnormalities such as benign prostatic hyperplasia (BPH) or prostate cancer may be more likely to present with prostatitis. In terms of presentation, acute bacterial prostatitis patients typically present with fever, dysuria, pelvic/lower back pain, and/or prostatic tenderness and swelling.[5] Those with chronic bacterial prostatitis usually have a history of recurrent UTIs. Patients may also complain of pain with ejaculation and sexual dysfunction. Pyuria and bacteriuria on urinalysis may be diagnostically useful if there are higher bacterial counts in the prostatic fluid compared to the urine but are seldom seen.

On the other hand, prostate cancer (PCa), which mainly consists of prostatic adenocarcinoma, is one of the most common cancers in men. It usually arises in the peripheral zone of the prostate. Most patients are brought to clinical attention due to PSA screening which tends to be elevated in both PCa and a number of other conditions complicating the picture. Diagnoses is primarily done via transrectal ultrasound-guided biopsy after suspicious digital rectal exam (DRE) finding on the posterior/lateral surface of the prostate, or abnormal PSA levels.[6] In fact, transrectal ultrasound is sometimes used to evaluate tumors found on DRE. However, it has a low specificity and is thus not used

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to guide the decision to biopsy.[7] Many clinicians at present use magnetic resonance imaging (MRI) to make that decision as it helps to characterize the primary tumor. In terms of staging, PCa is staged based on the Gleason grading system, which run between Grade 6 to 10 where 6 is low grade, 7 is intermediate, and anything above 8 is high grade. The latter was supplemented by the Epstein grading system with Grade Group 1 being favorable and Grade Group 5 being the most aggressive as in Grade Group 5 the specimen lacks gland formation.

Potential PCa symptoms, if any, are very nonspecific and may generally present similar to those of benign prostatic hyperplasia such as nocturia, urinary frequency, hesitancy, and dysuria. On the other hand, hematuria is generally associated with bladder cancer rather than PCa. Weight loss and bone pain develop as the disease progresses. However, most patients are asymptomatic especially in early disease. Age of >50 years old, family history, and high fat diet are the main risk factors. Moreover, certain ethnic groups such as Black Africans or Black Caribbeans are at a higher risk of prostate cancer.[8] Treatment options include active surveillance, radical prostatectomy, external beam radiation, brachytherapy, or androgen deprivation therapy, which is most often used for those with advanced disease.

According to the Canadian Cancer Registry database for the period of 2011–2015, approximately 74.4% of all prostate cancers were diagnosed at stages I and II. This indicates that cancer cases were detected early likely through ordering PSA levels in suspected patients in the initial workup. Only 8.6% of prostate cancers were diagnosed at stage IV.[9] Further, young males (aged 18 to 59 years old) had lower incidence rates across all stages with an age-specific incidence rate of 2.6 per 100,000 population at stage IV at diagnosis. This is compared to males aged 60–69 years old and 70–79 years old with an incidence rate of 33.9 and 64.1 per 100,000 population at stage IV, respectively. The latter finding is of no surprise as PCa is a disease of older men and as they grow older they tend to present with more advanced stages of the disease.

Prostate-Specific Antigen in the Context of Prostatitis and Cancer

Serum PSA tends to be elevated in all variants of prostatitis whether it is sterile or associated with active infection.[10] Hence, it is prudent not to order in these cases. In one randomized study, PSA returned to normal levels in approximately 50% of the patients following successful treatment.[11] Treatment generally includes using fluoroquinolones such as ciprofloxacin 500 mg po BID for 4–6 weeks. However, as mentioned above, PSA should not be ordered in the first place.

Normal PSA is <4.0 ng/mL but the actual value is inconclusive because no specified threshold to diagnose PCa was identified by studies.[12] In other words, a PSA level in the normal range for age does not by itself rule out PCa. Changes in PSA level over a period of time (i.e., PSA velocity) is a rather helpful clinical marker to monitor the likelihood of developing PCa.[13] Another clinical marker is PSA density. As a general rule of thumb, a prostate size to PSA level ratio (i.e., PSA density) of about 10:1 is normal.[14] For example, if the prostate size on ultrasound is 40cc, then a PSA of 4 ng/mL is normal. Yet another utility of measuring PSA is to determine the percentage of free or unbound PSA to total PSA ratio which tends to be low in PCa. This ratio can aid to distinguish PCa from BPH with one study claiming that a cutoff of ≤25% is more likely to be PCa than a benign condition.[15] However, an absolute percentage is controversial and its use is limited to certain scenarios.[16]

When a PSA cut-off of >4.0 ng/mL is used in screening for prostate cancer, approximately 70% of the biopsies come back negative.[17] However, of these negative biopsies, about 20–30% of the biopsied patients are false negatives and actually have cancer. These can be cancers of the anterior region of the prostate which are not biopsied as readily compared to the peripheral zone.[18] This illustrates the lack of reliability of using PSA and random biopsies to identify clinically significant cancers.[19] Therefore, multiparametric prostate magnetic resonance imaging (MP-MRI) using 3T scanner is now used in multiple centers to allow for closer examination of suspicious lesions. Moreover, using MRI-Ultrasound-fusion-guided biopsy which digitally overlays real-time ultrasound with MRI image slices allows for specific and accurately targeted biopsies. It also showed better detection for clinically significant prostate cancers by targeting certain tumors in the anterior region of the prostate.[20] Recently, some centers began utilizing the transperineal biopsy approach instead of the transrectal approach as it reduces the infection risk and may have better sampling of the anterior prostate.[21]

Lastly, it is worth mentioning that although PSA as a screening test is controversial due to its inherent inaccuracies, its use to detect recurrence post treatment is beneficial. In fact, its utility as an accurate biomarker for post surgical or radiation treatment is well established to identify biochemical recurrence prior to the development of symptoms.[22] A rise of PSA of ≥0.2 ng/mL after radical prostatectomy or 2 ng/mL or more above the nadir after radiation therapy are both considered biochemical recurrence of PCa by definition.[23,24] Nonetheless, PSA doubling time is another important variable to follow especially post radiotherapy to identify recurrence. It has been reported that patients with a PSA doubling time of <3 months are at high risk of death.[25]

Prostate Imaging Reporting and Data System (PI-RADS)

PI-RADS classification was designed recently to standardize MRI acquisition and reporting in order to improve the localization and characterization of those sus-

pected of having PCa.[26] The most recent version (PI-RADSv2.1) was released in 2019 thanks to advancements in multiparametric MRI as a novel tool that combines anatomical and functional imaging. Functional imaging includes T2-weighted, apparent-diffusion coefficient, diffusion weighted, and dynamic contrast-enhanced images in order to obtain an optimal three-dimensional image of the prostate.[27] In simple terms, PCa appears homogeneously hypointense (dark) on T2-weighted MRI images and generally enhances on gadolinium. The lesion appears focal, round, irregular, and restricted compared to prostatitis, which generally appears wedge-shaped, diffuse, and band-like in morphology.[26] However, the distinction is not often clear. This led some clinical researchers to introduce quantitative analysis of multiparametric MRI using pharmacokinetic parameters to differentiate PCa and prostatitis objectively.[28] Another group of researchers used machine learning algorithms to further improve the PI-RADS scores assigned by the uroradiologists.[29] In general, PI-RADS scores greater than 3 are usually considered suspicious for clinically significant cancer.[19] A PI-RADS score of 1 indicate that clinically significant PCa is highly unlikely, unlike a score of 5, which indicates that PCa is highly likely. A clinically significant PCa in this case is defined histologically as Gleason score $\geq$7. Lastly, it should be noted that PI-RADS does not have a role in the detection of recurrent PCa nor any role in detecting progression after therapy.

Protein Specific Membrane Antigen Positron Emission Tomography (PSMA PET)

One recent advancement in the detection of PCa metastasis is PSMA PET. PSMA is a protein that is overexpressed in prostate cancer cells. Gallium-68 PSMA-11 (^{68}Ga-PSMA-11) is the molecule that is injected in the arm of the patient to specifically bind the tumor cells giving off detectable radioactivity as the gallium decays. PSMA PET offers a sensitivity of 85% and a specificity of 98% compared to conventional imaging with CT and bone scans. Moreover, radiation exposure is less by 10.9 millisieverts (mSv).[30] For perspective, this is the equivalent of around 100 fewer chest x-rays per year. In 2020, the Food and Drug Administration (FDA) approved the ^{68}Ga-PSMA-11 tracer to detect metastasis in men with PCa and also in those who were successfully treated for PCa but suspected of having a recurrence due to elevated PSA levels.[31] Previously, fluciclovine PET was the standard of care but had a moderate specificity and performance at low PSA levels.[32] It also had approximately a 3:1 tumor to background intake ratio versus 50:1 now with PSMA PET, making it much easier to localize the lesion than before. PSMA PET also has a superior inter-reader agreeability compared to fluciclovine.[33] This is especially important for PSMA+ patients with recurrences after radical prostatectomy who present with PSA levels <2.0 ng/mL. In these patients, a recent study by the department of Radiation Oncology at the University of California found that 38% of cases would be missed by standard radiation therapy had ^{68}Ga-PSMA-11 PET not been used to detect those lesions prior to therapy.[34] It is important to also note that, where ^{68}Ga-PSMA is used as a radiotracer, PET lesion detection rate is positively correlated with higher PSA levels ($\sim$52% for <1.0 ng/mL vs. 91% >2.0 ng/mL).[35] This is due to reasons that are beyond the scope of this article. In summary, the value of PSMA PET lies in the detection of metastasis with high specificity in early biochemical recurrence.

Cost Analysis

Discussing PCa diagnosis and screening is not complete without discussing the cost and impact on quality of life. The effectiveness of early detection in prostate cancer is still a matter of debate that continues to challenge the experienced clinician. The dilemma is that early detection with PSA is contributing to overdiagnosis and overtreatment in patients. Discussing patient values, life expectancy, and goals is particularly important for such clinical enigmas. In addition, clinical correlation and professional judgment are essential when evaluating the need to further workup the patient and pursuing a biopsy. This is due to the lack of agreement between studies in terms of modeling prostate cancer progression. Additionally, most of these studies failed to follow the recommended methods in estimating quality of life and accounting for adverse treatment effects on benefits of life years gained.[36] A recent study in Sweden that looked at Cochrane data found that although PCa screening using MRI and targeted-biopsy improved sensitivity and specificity, it was classified as a very high cost per quality-adjusted life-year (QALY).[37] Specifically, the study found that using MRI PI-RADS had the most favourable diagnostic accuracy and detection when compared to systematic Transrectal ultrasound-guided biopsy.[38] Another model suggested that an optimum screening strategy is to biopsy patient with PI-RADS score of $\geq$3 but not those with a score of <3.[39] They determined that this strategy will provide an incremental cost-effectiveness ratio (ICER) of $23,483 per QALY.

According to the recent National Comprehensive Cancer Network (NCCN) guidelines, regarding the use of PSMA PET to rule out metastatic disease, those in the very low or low risk group (defined as having PSA <10 ng/mL beside other features) require no imaging while anyone in the intermediate risk group or above requires imaging.[40] Currently, NCCN does not specify PSMA PET in their guidelines for recurrent PCa. However, some experts argue that PSMA PET should be included in the guidelines because PSMA PET can affect the management of more than 50% of the patients scanned by upstaging or downstaging the disease.[41] It should be noted that PSMA PET is not widely available in Canada.

Conclusion

Non-invasive and minimally invasive diagnostic methods such as imaging are becoming more appealing in modern medicine to increase patient convenience and satisfaction. However, the clinician needs to examine the diagnostic sensitivity and specificity of such interventions to reduce the burden of misdiagnosis and disease progression, especially in the case of cancer where biopsy is needed to establish the diagnosis. MRI PI-RADS classification system offers a more sensitive and specific diagnostic tool to differentiate PCa from its mimics and inform the need to biopsy. Further, with the recent development of PSMA PET, clinicians can elucidate the recurrence of PCa with better sensitivities. However, further studies in regard to the use of these tools in the management, investigation, and treatment of PCa along with their impact on the quality of life are needed.

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