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EDITORIAL

Incorporating the [68Ga]Ga-PSMA PET/CT PRIMARY score into the selection criteria for prostate cancer patients eligible for active surveillance

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Active surveillance (AS) has become a preferred strategy to minimize overtreatment in patients with low-risk prostate cancer (PCa) who do not present with severe lower urinary tract symptoms. Identifying candidates for AS and monitoring them effectively is crucial to mitigate the risk of undertreating localized disease. Currently, the selection of patients for AS is based on a combination of digital rectal examination (DRE) results, prostate-specific antigen (PSA) levels, Gleason score from prostate biopsies, and the rate of tumor-positive biopsy cores. Some protocols also incorporate PSA density, the rate of cancer in biopsy cores, and multiparametric prostate magnetic resonance imaging (mpMRI) to enhance predictive accuracy. Despite these measures, the absence of universally accepted selection standards leads to inconsistencies in identifying appropriate AS candidates. These inconsistencies may result in unnecessary curative treatments, such as radical prostatectomy or radiotherapy for patients suitable for AS, or conversely, a missed opportunity for timely intervention in high-risk patients.

Follow-up protocols typically recommend an annual DRE, biannual PSA tests, and repeat biopsies at least once every 1 to 3 years. However, the invasive nature of prostate biopsies, which can cause discomfort and risks such as infections leading to sepsis, hematuria, hematospermia, and dysuria, often dissuades patients from undergoing repeat procedures [1, 2]. Adherence to the AS protocol is paramount for its success. The PRIAS study indicated that 40% of patients deviated from the protocol, opting for definitive treatments for reasons outside of the guidelines [3, 4]. Consequently, there is a pressing need for new, reliable, and preferably non-invasive diagnostic tools.

mpMRI pathway

mpMRI has significantly advanced the field by providing high-resolution anatomical sequences, diffusion-weighted imaging (DWI), and perfusion analyses. These techniques have refined the classification of patients and improved treatment outcomes by accurately visualizing clinically significant lesions. The Prostate Imaging Reporting and Data System (PI-RADS) scoring has standardized lesion assessment, facilitating clearer communication between radiologists and clinicians, with pathologic sampling of risky lesions deemed essential. Various biopsy techniques, such as MR-ultrasonography (US) fusion, cognitive fusion, and in-bore biopsy, have emerged, with literature suggesting comparable efficacy in lesion targeting [5]. Current clinical guidelines strongly advocate for an mpMRI prior to initial biopsy and before repeat biopsy following a negative transrectal ultrasound (TRUS)-guided biopsy, due to the modality's ability to visualize high Gleason score lesions and its high negative predictive value for clinically significant tumors [6, 7].

The ideal biopsy strikes a balance between accurate pathological classification and tumor extent detection while minimizing the number of cores required. mpMRI shows promise in achieving this balance. While mpMRI has limitations, guidelines suggest that combining targeted biopsy with standard biopsy in routine practice maximizes the detection of clinically significant tumors. Emerging research

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suggests that by integrating PSA density, clinical risk assessments, and mpMRI, the total number of biopsies required can be reduced. Although this mpMRI pathway has not yet been fully integrated into clinical guidelines, the literature continues to report its potential benefits.

Is there a [^{68} Ga]Ga-PSMA PET/CT pathway?

[^{68} Ga]-labeled prostate-specific membrane antigen inhibitor positron emission tomography/computed tomography ([^{68} Ga]Ga-PSMA PET/CT) has gained prominence for PCa staging and re-staging. Recently, its potential for diagnosing, particularly distinguishing between aggressive and indolent forms of PCa, is being considered. PSMA expression, which correlates with cancer grade and severity, can be visualized via this imaging technique. Elevated maximum standard uptake value (SUVmax) levels on [^{68} Ga]Ga-PSMA PET/CT scans have been associated with higher grade groups of PCa [8]. The PRIMARY study was designed to evaluate the effectiveness of [^{68} Ga]Ga-PSMA PET/CT compared to mpMRI in diagnosing clinically significant prostate cancer [9]. The findings suggest that combining mpMRI with [^{68} Ga]Ga-PSMA PET/CT greatly enhances sensitivity, reducing the rate of false negatives. This combination could potentially decrease the need for prostate biopsies when identifying csPCa. Nonetheless, there are drawbacks. Biopsy-based assessments may miss crucial diagnoses, and there is considerable overlap in SUVmax across PCa grades. Moreover, the screening application of [^{68} Ga]Ga-PSMA PET/CT alongside mpMRI can result in redundant testing.

The introduction of the PRIMARY score marks progress in initial PCa diagnosis. This score considers the uptake pattern within prostate gland, uptake presence in the peripheral zone, and uptake intensity, aiming to refine diagnostic accuracy. Reproducibility studies indicate that the PRIMARY score is on par with mpMRI in consistency and may predict csPCa effectively [10]. This raises the possibility of using [^{68} Ga]Ga-PSMA PET/CT as an alternative to repeat biopsies in diagnosing csPCa. Furthermore, [^{68} Ga]Ga-PSMA PET/CT could serve as a non-invasive diagnostic tool for csPCa and for monitoring patients under active surveillance (Fig. 1) [11]. However, since the PRIMARY score's data encompasses all cancer grades, its diagnostic performance and reproducibility are potentially inflated. Its efficacy in patients with International Society of Urological Pathology Grade Group 1 (ISUP 1) diagnosed via biopsy remains unclear, suggesting a need for further refinement of the PRIMARY score [12]. Consequently, the application of [^{68} Ga]Ga-PSMA PET/CT might expand beyond its conventional use in staging and re-staging of PCa.

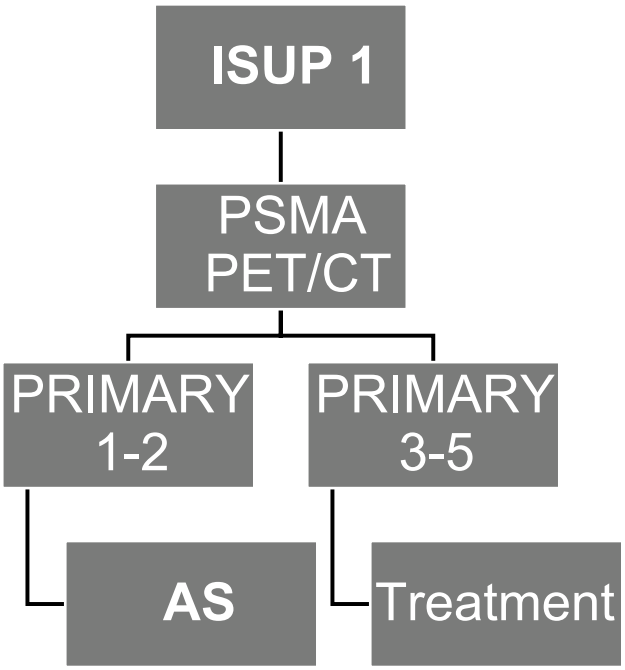

Fig. 1 Suggested protocol for incorporating [68 Ga]Ga-PSMA PET/CT into the patient selection process for active surveillance

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Declarations

Competing interests The authors declare no competing interests.

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