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INTEGRATED APPROACH TO THE DIAGNOSIS AND TREATMENT OF PROSTATE CANCER: FROM PSA SCREENING AND PROSTATE BIOPSY TO MRI, PSMA PET/CT AND RADICAL PROSTATECTOMY



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ABSTRACT

Prostate cancer diagnosis requires an integrated assessment of PSA, MRI, biopsy and PSMA PET/CT. This review summarizes the role of these methods in detecting clinically significant cancer, determining disease extent and selecting patients for radical prostatectomy. The combination of PSA-based risk assessment, multiparametric MRI and targeted biopsy improves diagnostic accuracy, while PSMA PET/CT provides additional information for staging high-risk disease. An individualized diagnostic pathway may improve treatment selection and reduce unnecessary interventions.

Keywords: prostate cancer; PSA; MRI; PSMA PET/CT.

АННОТАЦИЯ



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Диагностика рака предстательной железы требует комплексной оценки ПСА, МРТ, биопсии и ПСМА ПЭТ/КТ. В обзоре рассмотрена роль этих методов в выявлении клинически значимого рака, определении распространённости заболевания и выборе пациентов для радикальной простатэктомии. Сочетание оценки риска по ПСА, мультипараметрической МРТ и таргетной биопсии повышает точность диагностики, а ПСМА ПЭТ/КТ дополняет стадирование пациентов высокого риска. Индивидуализированный диагностический алгоритм способствует оптимальному выбору лечения.

Ключевые слова: рак простаты; ПСА; МРТ; ПСМА ПЭТ/КТ.

АННОТАЦИЯ

Простата беи саратони диагностикаси PSA, MPT, биопсия ва PSMA PET/КТ натижаларини комплекс баҳолашни талаб қилади. Ушбу обзorda клиник аҳамиятли ўсманни аниқлаш, касаллик тарқалишини баҳолаш ва радикал простатэктомия учун беморларни танлашда мазкур усулларнинг ўрни кўриб чиқилган. PSA асосидаги хавф баҳоси, мультипараметрик МРТ ва мақсадли биопсиянинг биргаликда қўлланилиши диагностика аниқлигини оширади, PSMA PET/КТ эса юқори хавфли беморларни стадиялашни такомиллаштиради. Индивидуал диагностик алгоритм даволаш тактикасини мақбул танлашга ёрдам беради.

Калит сўзлар: простата саратони; PSA; MPT; PSMA PET/КТ.

INTRODUCTION

Prostate cancer is one of the most common malignant diseases affecting men worldwide. Its clinical behavior is highly variable. Some tumors remain localized and biologically indolent for many years, whereas others demonstrate aggressive growth, early metastatic spread and a significant risk of cancer-specific mortality. This heterogeneity makes the initial diagnostic assessment particularly important. The objective of contemporary prostate cancer diagnostics is not simply to detect as many tumors as possible. The more relevant clinical objective is to identify clinically significant prostate cancer (csPCa), generally represented by tumors with a Gleason Grade Group of 2 or higher, while limiting unnecessary biopsies and avoiding overdiagnosis of clinically insignificant disease. Historically, the diagnostic pathway was largely based on serum prostate-specific antigen (PSA), digital rectal examination and systematic transrectal ultrasound-guided biopsy. Although this approach substantially increased the detection of prostate cancer, it also resulted in the diagnosis of a considerable number of low-grade tumors and exposed patients to unnecessary biopsy procedures.

The introduction of multiparametric magnetic resonance imaging (mpMRI) has changed this paradigm. As a result, biopsy can be directed toward lesions that have a higher probability of clinically significant disease. PSMA PET/CT is particularly relevant for staging patients with higher-risk disease and may identify pelvic nodal or distant metastases that are not apparent on conventional imaging. These developments have resulted in a more complex but potentially more precise diagnostic pathway. PSA, MRI, biopsy and PSMA PET/CT should not be viewed as competing investigations. Rather, each addresses a different clinical question. PSA provides an initial estimate of risk; MRI identifies and characterizes suspicious intraprostatic lesions; biopsy establishes histological diagnosis and grade; and PSMA PET/CT provides information about the extent of disease beyond the prostate.



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The purpose of this review is to evaluate the current evidence for integrating these diagnostic modalities and to discuss how the resulting information can be used to select patients for radical prostatectomy and other treatment strategies.

LITERATURE REVIEW

PSA AND EARLY DETECTION OF PROSTATE CANCER

PSA remains the most widely used biomarker for the early detection of prostate cancer. Its principal limitation is that it is prostate-specific rather than cancer-specific. PSA may be elevated in benign prostatic hyperplasia, prostatitis, urinary retention and other benign conditions. Therefore, PSA concentration alone cannot reliably determine whether a patient has clinically significant prostate cancer.

Long-term results from the European Randomized Study of Screening for Prostate Cancer have shown that PSA-based screening can reduce prostate cancer mortality, although the benefit is accompanied by a risk of overdiagnosis. In the 23-year follow-up, PSA screening was associated with a relative reduction in prostate cancer mortality, while the cumulative incidence of prostate cancer was higher among screened men [1].

These findings illustrate the principal limitation of conventional PSA screening. Increasing the number of biopsies does not necessarily translate into a proportional improvement in clinically meaningful cancer detection. For this reason, contemporary diagnostic strategies increasingly use PSA as the first step in a broader risk assessment rather than as an isolated indication for biopsy.

PSA density (PSA-D) has become particularly useful in this context. PSA-D is calculated by dividing serum PSA by prostate volume and provides an estimate of whether the PSA concentration is disproportionate to gland size. A higher PSA-D is associated with an increased probability of clinically significant cancer and is especially useful when MRI findings are negative or equivocal [2].

THE ROLE OF MULTIPARAMETRIC MRI

The introduction of mpMRI represents one of the major advances in prostate cancer diagnosis. MRI provides anatomical and functional information that cannot be obtained from PSA testing or conventional ultrasound.

The Prostate Imaging-Reporting and Data System (PI-RADS) was developed to standardize prostate MRI interpretation. Lesions are assigned a PI-RADS score from 1 to 5, reflecting the likelihood that clinically significant prostate cancer is present. In clinical practice, PI-RADS 4 and 5 lesions are considered particularly suspicious, whereas PI-RADS 1 and 2 findings are generally associated with a low probability of csPCa.

The PROMIS study provided important evidence supporting the use of mpMRI before biopsy. In this study, mpMRI demonstrated considerably higher sensitivity for clinically significant prostate cancer than standard transrectal ultrasound-guided biopsy [3]. The findings suggested that MRI could be used to identify men who were more likely to benefit from biopsy and potentially avoid unnecessary procedures in selected patients.

The PRECISION trial subsequently evaluated an MRI-based diagnostic pathway in biopsy-naïve men. Patients assigned to the MRI pathway underwent targeted biopsy when MRI showed a suspicious lesion, while men with non-suspicious MRI findings could avoid biopsy. Clinically



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significant prostate cancer was detected more frequently in the MRI-targeted group than in the standard biopsy group, while the detection of clinically insignificant cancer was reduced [4].

These findings have influenced current clinical practice. MRI is now widely considered an important examination before prostate biopsy in men with suspected clinically localized prostate cancer.

Nevertheless, a negative MRI does not completely exclude clinically significant disease. The probability of cancer after a negative MRI depends on the patient's PSA density and other risk factors. In particular, a high PSA density may indicate clinically significant disease even when the MRI is reported as PI-RADS 1 or 2.

Therefore, MRI results should be interpreted within the clinical context rather than treated as an independent diagnostic endpoint. The combination of PSA density, clinical risk factors and MRI findings provides a more reliable basis for deciding whether biopsy is necessary.

MRI-TARGETED AND SYSTEMATIC PROSTATE BIOPSY

Histopathological examination remains the basis for the definitive diagnosis of prostate cancer. In addition to confirming malignancy, biopsy provides information about Gleason pattern, ISUP Grade Group, tumor distribution and the extent of involvement of individual cores. These parameters are essential for subsequent risk stratification.

The development of MRI-targeted biopsy has addressed one of the principal weaknesses of conventional systematic biopsy. Traditional systematic sampling is performed without precise knowledge of the location of the tumor. Consequently, clinically significant lesions may be missed, particularly when they are located in the anterior or apical regions of the prostate.

MRI-targeted biopsy can be performed using cognitive targeting, MRI-ultrasound fusion systems or direct in-bore MRI guidance. The choice of technique depends on institutional resources and operator experience.

An important question is whether targeted biopsy can completely replace systematic sampling. Evidence suggests that this may not be appropriate in all patients.

In a prospective study comparing MRI-targeted, systematic and combined biopsy, Ahdoot et al. demonstrated that the combination of targeted and systematic biopsy identified more clinically significant cancers than either method alone [5]. In particular, systematic biopsy occasionally detected clinically significant disease outside the MRI-targeted lesion.

These findings are clinically important because the information obtained from biopsy is subsequently used to determine whether a patient is suitable for active surveillance, definitive local treatment or systemic therapy.

The optimal biopsy strategy therefore depends on the clinical setting. In a biopsy-naïve patient with a suspicious MRI lesion, targeted sampling should be performed, while additional systematic or perilesional cores may provide useful information about the overall tumor burden. In patients with previous negative biopsy but persistent suspicion, MRI-targeted biopsy becomes particularly valuable.



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The biopsy route has also received increasing attention. Transperineal biopsy is associated with a lower risk of infectious complications compared with the traditional transrectal approach and is increasingly preferred where appropriate expertise and equipment are available.

PSMA PET/CT IN THE STAGING OF PROSTATE CANCER

PSMA PET/CT has introduced molecular imaging into the routine management of prostate cancer. PSMA is highly expressed on the surface of most prostate cancer cells, particularly in clinically significant and aggressive tumors. Radiolabeled PSMA ligands allow visualization of prostate cancer lesions using PET imaging.

The clinical role of PSMA PET/CT should be distinguished from that of prostate MRI. MRI is primarily focused on the prostate and pelvis and is particularly useful for lesion detection and local staging. PSMA PET/CT, in contrast, provides whole-body information and is therefore especially useful when lymph-node or distant metastatic disease is suspected.

The proPSMA randomized trial provided strong evidence for the superiority of PSMA PET/CT over conventional imaging in men with high-risk prostate cancer. In this study, PSMA PET/CT demonstrated greater accuracy for detecting pelvic nodal or distant metastatic disease than conventional CT and bone scintigraphy [6]. Importantly, PSMA PET/CT also resulted in changes in clinical management in a substantial proportion of patients.

This has direct implications for patients being considered for radical prostatectomy. A patient who appears to have localized disease on conventional imaging may be found to have nodal or distant lesions on PSMA PET/CT. Such findings may alter the treatment strategy and prevent inappropriate use of surgery as an isolated treatment.

At the same time, PSMA PET/CT has limitations. Small-volume nodal metastases may remain below the spatial resolution of PET imaging, and a negative PSMA PET/CT cannot exclude microscopic disease. Therefore, PSMA PET/CT should not be interpreted as a substitute for pathological staging.

The available evidence supports the strongest use of PSMA PET/CT in unfavorable intermediate-risk, high-risk and locally advanced prostate cancer, particularly when definitive local treatment is being considered.

RADICAL PROSTATECTOMY IN THE CONTEMPORARY DIAGNOSTIC PATHWAY

Radical prostatectomy remains a major curative treatment for patients with localized prostate cancer and is also considered in selected patients with locally advanced disease.

The increasing use of MRI and PSMA PET/CT has changed the way patients are selected for surgery. Modern prostatectomy planning increasingly incorporates information about the location of the tumor, suspected extracapsular extension, seminal vesicle involvement and nodal or distant disease.

For patients with localized disease and a sufficiently long life expectancy, radical prostatectomy offers the possibility of definitive local control. However, treatment decisions should take into account the risk of postoperative urinary incontinence, erectile dysfunction and other complications.

Nerve-sparing surgery can improve the probability of postoperative erectile function when oncologically appropriate. However, preservation of the neurovascular bundles should not be



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performed at the expense of cancer control when there is significant suspicion of extracapsular extension.

The development of robotic-assisted radical prostatectomy has further improved the technical possibilities of minimally invasive surgery. Enhanced visualization and instrument dexterity may facilitate precise dissection, although the fundamental oncological principles of radical prostatectomy remain unchanged.

The results of the ProtecT trial provide an important perspective on treatment selection. After 15 years of follow-up, prostate cancer-specific mortality was low among men assigned to active monitoring, surgery or radiotherapy, although active monitoring was associated with a higher risk of disease progression and metastasis [7].

These findings underline an important principle: the presence of prostate cancer does not automatically mean that radical treatment is necessary. The decision should reflect tumor biology, life expectancy, patient preference and the expected balance between oncological benefit and treatment-related morbidity.

INTEGRATED DIAGNOSTIC AND TREATMENT ALGORITHM

Based on the available evidence, a practical diagnostic pathway can be summarized as follows:

Step 1. Initial assessment

PSA should be obtained in appropriately selected men after discussion of the potential benefits and limitations of prostate cancer screening. Clinical history, family history, previous biopsy results and life expectancy should also be considered.

Step 2. Risk assessment

When PSA is elevated, the result should be interpreted in context. Repeat PSA may be appropriate when clinically indicated. PSA density should be calculated after determination of prostate volume.

Step 3. Multiparametric MRI

Patients with persistent suspicion of clinically significant prostate cancer should undergo mpMRI before biopsy when appropriate.

Step 4. Biopsy decision

The decision to biopsy should incorporate PI-RADS category, PSA density and clinical risk factors.

Step 5. MRI-targeted biopsy

Patients with suspicious MRI lesions should undergo targeted biopsy. Additional systematic or perilesional sampling should be considered according to the clinical setting.

Step 6. Histological risk stratification

The pathology report should include Gleason score/ISUP Grade Group and relevant information concerning tumor extent and adverse histological features.

Step 7. Staging



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PSMA PET/CT should be considered when the estimated risk of nodal or distant disease is sufficiently high, particularly in unfavorable intermediate-risk, high-risk and locally advanced disease.

Step 8. Treatment selection

The final treatment decision should integrate clinical stage, PSA, Grade Group, MRI findings, PSMA PET/CT findings, life expectancy, comorbidities and patient preferences.

Step 9. Definitive treatment

Radical prostatectomy is an appropriate option for selected patients with localized or selected locally advanced disease. Radiotherapy-based treatment and active surveillance remain important alternatives depending on risk group.

ANALYSIS AND DISCUSSION

The evidence reviewed in this article supports a shift from a linear diagnostic model toward an integrated risk-adapted pathway.

The traditional model can be summarized as:

Elevated PSA → systematic biopsy → diagnosis → treatment.

The contemporary model is more accurately represented as:

PSA → risk assessment → MRI → targeted biopsy ± systematic sampling → pathological risk stratification → PSMA PET/CT when indicated → individualized treatment.

The difference between these two models is clinically important. In the traditional approach, biopsy was frequently performed primarily on the basis of PSA elevation. In the modern approach, MRI and additional risk parameters can help identify patients in whom biopsy is more likely to provide clinically useful information.

MRI has therefore become a central component of the pre-biopsy pathway. Nevertheless, MRI should not be interpreted in isolation. A negative MRI in a patient with a markedly elevated PSA density does not carry the same significance as a negative MRI in a patient with low PSA density and otherwise low clinical suspicion.

The same principle applies to PSMA PET/CT. Its strength lies in identifying disease outside the prostate, but its sensitivity is insufficient to exclude microscopic metastatic involvement. Consequently, a negative PSMA PET/CT should not be regarded as proof of pathologically node-negative disease.

The value of integrating these modalities becomes particularly apparent in patients being considered for radical prostatectomy. The decision to operate should be based on the estimated probability that the tumor remains amenable to curative local treatment.

For example, a patient with a suspicious MRI lesion, biopsy-confirmed Grade Group 4 disease and no evidence of metastasis on PSMA PET/CT may remain a candidate for radical prostatectomy within a multimodal treatment strategy. Conversely, the identification of distant PSMA-avid metastases may substantially alter the balance between surgery and systemic treatment.



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Another important issue is the prevention of overtreatment. The ability of MRI and PSMA PET/CT to detect more lesions should not be interpreted as a reason to treat every detected lesion aggressively. Better imaging should ultimately lead to better risk discrimination.

The integration of diagnostic information should therefore have two simultaneous objectives: earlier identification of clinically significant disease and avoidance of unnecessary intervention in patients with biologically insignificant tumors.

CONCLUSION

The contemporary diagnosis and treatment of prostate cancer increasingly relies on the integration of biochemical, anatomical, histological and molecular information.

PSA remains the starting point of early detection but should be interpreted within an individualized risk assessment rather than used as an isolated biopsy threshold. PSA density is particularly useful when assessing the probability of clinically significant cancer in combination with MRI findings.

Multiparametric MRI has become a key examination before prostate biopsy. It improves lesion localization, supports targeted sampling and provides valuable information about local tumor extent. However, a negative MRI cannot completely exclude clinically significant disease, and biopsy decisions should incorporate PSA density and other risk factors.

MRI-targeted biopsy improves the detection of clinically significant prostate cancer, while combined targeted and systematic or perilesional sampling may be appropriate in selected patients to reduce the risk of missing clinically important disease.

PSMA PET/CT adds whole-body molecular information and has particular clinical value in patients with unfavorable intermediate-risk, high-risk and locally advanced disease. Its role is especially important before definitive treatment when accurate staging may change the treatment strategy.

Radical prostatectomy remains an established curative option for appropriately selected patients. Modern patient selection should incorporate PSA, MRI, biopsy pathology and, when indicated, PSMA PET/CT rather than relying on any single diagnostic parameter.

The most appropriate contemporary strategy can therefore be summarized as:

PSA and clinical risk assessment → mpMRI → individualized biopsy → pathological risk stratification → PSMA PET/CT when indicated → multidisciplinary treatment selection.

Such an integrated approach has the potential to improve the detection of clinically significant prostate cancer, reduce unnecessary biopsies and avoid inappropriate treatment, while preserving the opportunity for curative treatment in patients with aggressive but potentially localized disease.

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