ORIGINAL RESEARCH ARTICLE

On Public Health and New Prostate Cancer Screening Strategies: Comparison of Methods and Results for Prevention

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Keywords: Prostate Cancer, Prostate-Specific Antigen, PCa Diagnosis, PCa Screening. Public Health;

ABSTRACT

Introduction: Prostate cancer (PCa) is one of the leading causes of death among men worldwide. Early detection is crucial for effective treatment, and several screening strategies have been developed to improve diagnostic accuracy and reduce false positives. This study compares new prostate cancer screening strategies, assessing their effectiveness, accuracy, cost-effectiveness and impact on patients' quality of life.

Methods: This comparative observational study analyzed clinical data from men aged 50 to 75 years without a previous diagnosis of prostate cancer. A literature search was conducted to determine advances in diagnosis and treatment efficacy.

Results: The results showed that the combination of PSA and multiparametric MRI increased diagnostic accuracy and reduced false positives. Liquid biopsy was a promising, less invasive tool with potential for early detection. In terms of cost-benefit, the multimodal approach proved to be advantageous, considering the costs of subsequent examinations and treatments, as well as the impacts on patients' quality of life.

Conclusion: New prostate cancer screening strategies have distinct advantages and limitations. Combining methods significantly improves clinical outcomes, reducing mortality and promoting a better quality of life for patients. This study highlights the importance of a multimodal approach to prostate cancer screening and the need for continued research to validate these strategies in different populations and clinical settings.

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What do we already know about this topic?
It is well known that prostate cancer screening strategies have evolved significantly in recent years. Traditionally, prostate-specific antigen (PSA) testing has been widely used, but it has limitations, such as low specificity, leading to overdiagnosis and unnecessary treatment.
Recently, new approaches have been developed to improve screening accuracy. These include the use of biomarkers and multiparametric magnetic resonance imaging (mpMRI). Clinical trials, such as STHLM3-MRI, have shown that combining biomarkers with mpMRI can increase the detection of clinically significant cancers and reduce the need for unnecessary biopsies. In addition, the use of risk calculators and the selection of men with elevated PSA for lesion-directed biopsies rather than systematic biopsies have shown potential to reduce the detection of low-grade cancers and, consequently, overdiagnosis. These improvements have led to recommendations for assessing the feasibility and effectiveness of organized prostate cancer screening programs in the European Union. In summary, novel screening strategies for prostate cancer that combine biomarkers, mpMRI, and targeted approaches offer significant promise for improving diagnostic accuracy and reducing adverse effects associated with overdiagnosis and overtreatment.
What is the main contribution to Evidence-Based Practice from this article?
The main contribution of this article to evidence-based practice is the introduction and comparison of new screening strategies for prostate cancer, which combine the use of biomarkers and multiparametric magnetic resonance imaging (mpMRI). The combination of these techniques has the potential to significantly improve diagnostic accuracy, reducing overdiagnosis and unnecessary treatments associated with prostate-specific antigen (PSA) testing. By comparing different screening methods and presenting robust evidence on their advantages and disadvantages, the article provides a solid basis for implementing these new approaches in clinical practice. This may lead to more accurate and effective screening, improving outcomes for patients with prostate cancer. In addition, the article highlights the importance of personalizing screening protocols, taking into account individual risk factors and using advanced technologies to optimize diagnosis. This evidence-based approach promotes more informed and effective medical practice, resulting in better patient outcomes and more efficient use of health care resources.
What are this research's implications towards health policy?
This article on new screening strategies for prostate cancer has important implications for theory, practice and policy.
Theory: The article reinforces the theoretical understanding that combining biomarkers and multiparametric magnetic resonance imaging (mpMRI) can increase screening accuracy and reduce overdiagnosis. This supports the theory that more sophisticated and integrated methods can significantly improve diagnostic outcomes. Practice: In clinical practice, the article provides robust evidence that can be adopted by oncologists and radiologists. The introduction of these new screening strategies can lead to more accurate detection of clinically significant cancers, reducing the number of unnecessary biopsies and overtreatments. This results in better patient outcomes and more efficient use of healthcare resources. Policy: In terms of healthcare policy, the article may influence prostate cancer screening guidelines and policies. The adoption of evidence-based strategies can lead to the implementation of more effective and efficient screening programmes, potentially resulting in improved public health outcomes and cost-effectiveness. These implications highlight the importance of the article in promoting advances in prostate cancer screening, benefiting patients, healthcare professionals and healthcare systems as a whole.

Authors' Contributions Statement:
Moraes, Vinicius Resende, lead author, wrote the introduction and methodology. Ribeiro, Lucas da Silva, co-author, wrote the introduction and results. Uniat, Kelly Cristina, co-author, wrote the methodology and results. Santos, Ysabel, co-author, wrote results and conclusion.

Introduction

Prostate cancer (PCa) is the most commonly diagnosed malignancy among men worldwide (1.4 million cases) (Zhang et al., 2022). Worldwide, the odds of developing PCa are 1 in 16, ranging from 1 in 56 in low-medium Sociodemographic Index (SDI) countries to 1 in 7 in high-SDI countries (Zhang et al., 2022). According to the American Cancer Society Cancer Statistics Reports (Siegel, Miller, & Jemal, 2018), there were an estimated 238,530 new diagnoses of PCa and an estimated 34,130 deaths from PCa in developed countries such as the United States in the year 2021. Center et al. predicted that the international burden of PCa is expected to grow to 1.7 million new cases and 499,000 new deaths by 2030, simply due to global population growth and ageing (Center et al., 2012).

The increased burden of PCa has also been observed in Asian countries, where PCa incidence rates were previously low. However, data on PCa incidence and mortality rates in some Asian countries are limited (Kimura & Egawa, 2018, Sakamoto, 2018). Reported incidence rates in some Asian countries may

also be statistically biased by the comprehensive implementation of early detection systems and the accuracy of national cancer registration systems, which are still immature in most Asian countries (Kimura & Egawa, 2018). So far, it has been shown that the prevalence of latent and incident PCa in contemporary Japan and Korea is similar to that in Western countries (Kimura & Egawa, 2018).

Interestingly, the incidence rate of PCa is markedly higher among Asian-American individuals compared with native Asian people. This may be partly explained by differences between Western and Asian diets. A large prospective cohort study of Japanese men conducted by the Japan Public Health Center stated that Westernized dietary pattern was associated with a higher risk of PCa diagnosis. Furthermore, according to Han et al., the prevalence of PCa in South Korea has increased significantly and will continue to increase, mainly due to the increase in its incidence rate, which can be attributed to the Westernization of dietary habits and rapid population ageing in South Korea (Han et al., 2015).

In addition, PCa in Korean men has been reported to be more aggressive, with lower 5-year biochemical recurrence-free survival (BCRFS) rates, higher pathological stages and grades, and poorer disease progression (extracapsular extension, seminal vesicle invasion, or Gleason score ⩾8), compared with PCa in Western populations (Han et al., 2015). Furthermore, regardless of initial serum PSA levels or clinical stages at presentation, a significant proportion of prostate cancers in Korean men exhibit poor differentiation, causing a higher PSA failure rate. Younger patients with PCa did not show more favourable pathologic features in RP specimens and showed similar BCR rates compared with older men in Korea (Han et al., 2015).

Comparison of the current clinicopathological features of PCa between American and Chinese men is lacking, although the incidence rate of PCa in China has been increasing annually (Ye & Zhu, 2015). The incidence rate of PCa is increasing particularly rapidly in urban areas of China, and mortality rates are high in rural areas of China. With the rapid development of China's economy and the improvement of people's quality of life, dietary habits and lifestyles have gradually been Westernized (Migowski & Silva, 2010), which may have contributed to the increase in the incidence rate of PCa in China. Researchers reported that the incidence of PCa was lower in Chinese cohorts than in Western cohorts at any prostate-specific antigen (PSA) level (Ye & Zhu, 2015). Further investigation into the clinicopathological features and molecular patterns of PCa in Chinese men may help to optimize the detection, risk stratification, and management of PCa. It has been reported that the overall survival rate of PCa in China is lower than that reported in other developed countries (Ye & Zhu, 2015).

Methodology

This is a comparative observational study involving the retrospective analysis of clinical data collected from patients undergoing different PCa screening methods with the aim of comparing different PCa screening methods and evaluating their results in terms of efficacy, diagnostic accuracy, cost-benefit, and impact on patient's quality of life.

The search for articles took place from January to February 2025, using the following national and international databases: MEDLINE (Medical Literature Analysis and Retrieval System Online /PubMed), EMBASE (Elsevier), CENTRAL (The Cochrane Central Register of Controlled Trials The Cochrane Library), Caribe/BVS – Virtual

Health Library, Scielo, Clinical Trials. Google Scholar was also used, with the same terms and strategies.
The following inclusion criteria were used to select the articles: full-text articles and original articles available in the selected databases, without restrictions on language and year of publication. Descriptive-observational, cross-sectional and experimental studies were included; prospective or retrospective, whose target audience was men aged between 50 and 75 years, without a previous diagnosis of prostate cancer, who had undergone screening exams at partner health institutions. Studies that did not mention which screening method diagnosed the patient with PCa, were female, did not include the established age and studies with patients who had already been previously diagnosed with prostate cancer were excluded. Studies that were available only in abstracts and studies with designs different from those described in the inclusion criteria were excluded.
After searching the databases, the results found were coupled to Microsoft Excel® and the articles were screened by carefully reading the full text.

Results

Germline mutations can lead to the development of aggressive PCa. Therefore, the following men should be considered for germline testing:

- Men with BRCA mutations on somatic testing.
- Men with multiple family members diagnosed with clinically significant PCa (cPCa) aged <60 years or a family member who died of PCa.
- Men with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.

A wide variety of exogenous/environmental factors have been discussed as being associated with the risk of developing PCa or as being aetiologically important for the progression of latent PCa to clinical PCa. However, there are currently no known effective preventive dietary or pharmacological interventions. Hypogonadal men who receive testosterone supplements do not have an increased risk of developing PCa (Haider et al., 2015). Furthermore, although the evidence is limited, men who are treated expectantly for PCa, or who have received radical curative therapy, do not have worse outcomes when receiving testosterone supplementation, despite a theoretically higher risk of progression after correction of the hypogonadal situation (Golla & Kaplan, 2017). The 2017 Union for International Cancer Control tumour, node and metastasis (TNM) classification, eighth edition, for staging PCa should be used (Brierley, Gospodarowicz & Wittekind, 2017). cT staging has been based solely on digital rectal examination (DRE); however, changes in the diagnostic pathway, particularly the introduction of imaging techniques such as magnetic resonance imaging (MRI), prostate-specific membrane antigen (PSMA) positron emission tomography (PET) and targeted biopsy, are causing a stage shift in the risk group distribution, and this should be taken into account when making treatment decisions. The EANM has recently proposed a molecular imaging TNM (miTNM) classification, using PSMA PET/computed tomography (CT) findings (Ceci et al., 2021). The prognosis of the miT, miN and miM substages is likely to be better than their T, N and M counterparts because PSMA PET/CT is more sensitive than the usual bone scan and abdominopelvic CT-based examination. The extent of this prognostic shift remains to be assessed, as well as its practical interest and

impact. The ISUP 2005 Gleason score (GS), together with its 2014 and 2019 modifications, is the recommended PCa grading system (Epstein et al., 2016; Van der Kwast et al., 2011).

The biopsy GS consists of the Gleason grade of the most extensive pattern plus the highest pattern, regardless of its extent. In addition to reporting the carcinoma characteristics for each biopsy side, an overall (or global) GS based on the carcinoma-positive biopsies should be provided. For targeted and regional biopsy cores of a lesion, this overall GS for the combined cores should be used. In radical prostatectomy (RP) specimens, the GS is determined differently: a pattern comprising 5% of the cancer volume is not incorporated into the GS, but its proportion should be reported separately if it is grade 4 or 5 (Van der Kwast et al., 2011). The 2019 ISUP Gleason Grading Conference on the Gleason grading of PCa (Van der Kwast et al., 2011) supported the concept of grading groups, eliminating the anomaly that the least aggressive PCa has a GS of 6 and highlighting the clinical differences between GS 3+4 and 4+3 as shown in Table 1

Table 1. 2014 International Society of Urological Pathology grading system (groups)

Gleason Score	ISUP Notes Group
2-6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4, 3 + 5 ou 5 + 3)	4
9-10 (4 + 5, 5 + 4 ou 5 + 5)	5

ISUP = International Society of Urological Pathology. Source: The Author

The D'Amico risk group classification is based on grouping patients at similar risk of biochemical recurrence (BCR) after local treatment. However, it is becoming clear that subdividing intermediate-risk disease into ISUP grade groups is clinically useful. The Cambridge Prognostic Groups use a five-tier model based on ISUP grade group, PSA, and cT stage, and have been shown to have significantly better discriminative performance than the current three-tier risk groups for the most clinically relevant outcome of PCa-specific mortality (Gnanapragasam et al., 2016). This model separates the intermediate- and high-risk groups into clinically relevant subgroups and has been validated in separate cohorts (Gnanapragasam et al., 2016, Gnanapragasam et al., 2018).

Screening and early detection

The diagnostic pathway for PCa aims to detect significant PCa promptly while leaving insignificant PCa undetected, balancing diagnostic accuracy with the burden on the individual and healthcare provider. Patient-specific factors such as ethnicity, family history, age and comorbidity should always be considered.

Localized PCa is often asymptomatic. Individual requests for PSA testing may be considered after a discussion of the rationale and risk of identifying insignificant cancer. Local progression may cause symptoms such as lower urinary tract symptoms, erectile dysfunction (ED), retention, pain or haematuria. Bone metastases may cause pain or spinal cord compression. Definitive diagnosis usually relies on histopathological verification of prostate biopsy cores. However, men with a high suspicion of malignancy (e.g. a malignant-feeling prostate and PSA >100 ng/ml) and a positive bone scan may avoid a biopsy, especially if pre-existing comorbidities preclude second-line treatment. PCa screening remains one of the most controversial topics in the urological literature. The co-primary objectives are a reduction in disease-specific mortality and maintenance of quality of life (QoL). A Cochrane review of randomized PCa screening trials with PCa mortality as an outcome was updated in 2018 (Ilic, et al., 2018). The main conclusions of the updated publication from the results of five randomized controlled trials (RCTs) randomizing >721 718 men are as follows:

- Screening is associated with an increased diagnosis of PCa (incidence ratio [IR]: 1.23, 95% confidence interval [CI]: 1.03-1.48).
- Screening is associated with the detection of more localized disease (RR: 1.39, [1.09-1.79]) and less advanced PCa (T3-4, N1, M1; RR: 0.85 [0.72-0.99]).
- No PCa-specific survival benefit was observed (RR: 0.96 [0.85-1.08]). This was the primary outcome in all trials.

However, the largest study—the population-based European Randomized Trial of Screening for Prostate Cancer (ERSPC), which included >182 000 men, showed a significant reduction in PCa mortality in the screening arm (RR: 0.79; 95% CI: 0.69–0.91) (Hugosson et al., 2019). In the Gothenburg screening trial, with 18 years of follow-up, the proportion of PCa death for the screening group compared with the control group was 0.65 (95% CI: 0.49–0.87), and for men who started screening at 55–59 years, it was 0.47 (95% CI: 0.29–0.78) (Hugosson et al., 2018). The number needed to invite was 231; the number needed to diagnose (NND) was 10. In the Rotterdam section of the ERSPC, with 21 years of follow-up, the hazard ratio for death due to PCa was 0.73 in the screening group, with the number needed to invite of 246 and the NND of 14 to prevent one death due to PCa. To prevent one metastatic case, the number needed to screen was 121 and the NND was 7 (Hugosson et al., 2018).

Optimal intervals for PSA testing are unknown. The proposal is a 2-year interval for men at increased risk (e.g. PSA 2–3 ng/ml), while it could be expanded to up to 8 years for those without risk (e.g. PSA <1 ng/ml). The age to stop early diagnosis should be based on the individual's life expectancy, where comorbidity is as important as age. Men with a life expectancy <15 years are unlikely to benefit from any form of early diagnosis. Despite improvements, the diagnostic algorithm may still lead to overdiagnosis. Breaking the binding link between diagnosis and active treatment is the only way to decrease the risk of overtreatment while maintaining the potential benefit of individual early diagnosis for men who request it (Hugosson et al., 2018).

Diagnostic tools

The different diagnostic tools available can be used separately, or in combinations of various levels, to indicate the need for prostate biopsy. An abnormal DRE is an indication for biopsy, but as an independent variable, PSA is a better predictor of cancer than DRE or transrectal ultrasound (TRUS). PSA is a continuous parameter, with higher levels indicating a

higher likelihood of PCa, precluding an ideal PSA threshold for detecting nonpalpable but clinically significant PCa. A limited elevation of PSA alone should be confirmed after a few weeks under standardized conditions (i.e., no ejaculation, manipulations, or urinary tract infections) in the same laboratory before considering further testing (Hugosson et al., 2018). Risk calculators developed from cohort studies may also be useful to reduce further testing. Prostate-specific antigen density (PSA-D; serum PSA divided by prostate volume) can also help predict the presence of csCaP, especially in smaller prostates, using a cutoff of 0.15 ng/ml/cc. It is certainly one of the strongest predictors in risk calculators, and together this may allow men to avoid the need for biopsy (Hugosson et al., 2018).

Multiparametric magnetic resonance imaging (mpMRI) is increasingly important for biopsy optimization. In a Cochrane meta-analysis comparing magnetic resonance imaging (MRI) with template biopsies (⩾20 cores) in biopsy-naive and repeat biopsy settings, MRI had pooled sensitivity and specificity of 0.91 (95% CI: 0.83–0.95) and 0.37 (95% CI: 0.29–0.46) for ISUP grade 2 cancers and 0.95 (95% CI: 0.87–0.99) and 0.35 (95% CI: 0.26–0.46] for ISUP grade 3 cancers, respectively. In biopsy-naive men, an MRI-based indication for biopsy after referral leads to lower biopsy rates, fewer men diagnosed with PCa labelled as insignificant, and more men diagnosed with PCa labelled as PCa compared with systematic biopsy alone. This is also true in men with a negative biopsy. Combining PSA-D and MRI may also be useful. Based on a meta-analysis of >3000 biopsy-naïve men, a risk-adapted data table for csCaP was developed, linking Prostate Imaging Reporting and Data System (PI-RADS) scores (1–2, 3, and 4–5) to PSA-D categories (<0.10, 0.10–0.15, 0.15–0.20, and >0.20 ng/mL) (Schoots & Padhani, 2020). This risk-adapted matrix table can guide the decision to perform a biopsy.

The Stockholm test is a prediction model that relies on several clinical variables (age, first-degree family history of PCa, and prior biopsy), blood biomarkers (total PSA, free PSA, free PSA to total PSA ratio, human kallikrein 2, macrophage inhibitory cytokine 1, and microseminoprotein-β [MSMB]), and a polygenic risk score to predict PCa risk with an ISUP grade group ⩾2, and has been shown to reduce the percentage of clinically insignificant cancers when used in combination with MRI in a PSA screening population. It also has the potential to decrease the number of mpMRI scans required in PCa screening (Schoots & Padhani, 2020).

Although primarily used for staging purposes, prostate PSMA PET/CT (or PSMA PET/MRI) expression can be used to indicate and direct biopsies. For csCaP detection, pooled sensitivity of 0.89 and pooled specificity of 0.56 have been reported. In a prospective study of 291 patients, the combination of PSMA + MRI improved the negative predicted value compared with MRI alone (91% vs 72%, test ratio = 1.27 [1.11–1.39], $p < 0.001$). Sensitivity was also improved (97% vs 83%, $p < 0.001$), but specificity was reduced (40% vs 53%, $p = 0.011$) (Schoots & Padhani, 2020).

Prostate biopsy

US-guided prostate biopsy is the standard of care under local anaesthesia. For systematic biopsies, where no prior imaging is used for targeting, sampling sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland, collecting 12 cores. Where MRI has shown a suspicious lesion, adding targeted biopsy to systematic biopsy in biopsy-naïve patients increases the number of detected cases of ISUP grade ⩾2 and grade ⩾3 PCa by approximately 20% and

30%, respectively. In the setting of repeat biopsy, adding targeted biopsy to MRI increases the detection of ISUP grade ⩾2 and grade ⩾3 PCa by approximately 40% and 50%, respectively (van der Leest et al., 2019). An MRI-guided biopsy can be achieved using cognitive guidance, US/MRI fusion software, or direct borehole guidance, as inappropriately trained individuals there appears to be no difference between the techniques in detecting cancer. It may also be possible to avoid systematic biopsies entirely by including perilesional/regional biopsies. A meta-analysis of eight studies showed a non-significant difference in the detection of ISUP grade ⩾2 cancers in the MRI-guided regional and targeted biopsy approaches compared with the recommended practice of MRI-guided systematic plus targeted biopsy approach (RR: 0.95, 95% CI: 0.90–1.01; p = 0.09). However, the MRI-guided regional and targeted biopsy approach detected significantly more ISUP grade ⩾2 cancers than MRI-guided biopsy alone (RR: 1.18, 95% CI: 1.10–1.25; p < 0.001). This difference is small for PI-RADS 5 lesions. Furthermore, regional and MRI-targeted biopsy approaches may miss 12–17% of insignificant cancers (ISUP grade group 1) detected by the classical combined approach (Noujeim et al., 2023).

Prostate biopsy can be performed via the transperineal or transrectal approach. The only systematic review (SR) and meta-analysis comparing MRI-targeted transrectal biopsy with MRI-targeted transperineal biopsy, analyzing eight studies, showed greater sensitivity for detection of csCaP when the transperineal approach was used (86% vs 73%). This benefit was especially pronounced for anterior tumours. It is associated with increased patient discomfort, but evidence also suggests a reduced risk of infection with the transperineal route so antibiotic prophylaxis may not be necessary. This may be important after the European Commission implemented strict regulatory conditions regarding the use of fluoroquinolones, resulting in the suspension of the indication for perioperative antibiotic prophylaxis, including prostate biopsy (Noujeim et al., 2023). Each biopsy site should be reported individually, including its location, GS, ISUP grade group, and extent. If identified, lymphovascular invasion and extraprostatic extension (EPE) should be reported, as well as intraductal carcinoma and invasive cribriform pattern, as they represent independent factors for metastasis and cancer-specific survival (CSS). Clinicians and patients should note that MRI-targeted biopsy is more sensitive than systematic biopsy in detecting areas of high-grade cancer; as a consequence, ISUP grade group ⩾2 cancers detected by MRI-targeted biopsy are, on average, of better prognosis than those detected by systematic biopsy alone. When long-term follow-up of patients undergoing MRI-targeted biopsy becomes available, a revision of the risk group definition will become necessary. In the meantime, MRI-targeted biopsy results should be interpreted in the context of this potential grade change (Ploussard et al., 2020).

PCa Staging

The decision to proceed with further staging is guided by the available treatment options, taking into account patient preference and comorbidity (Table 2).

Table 2. Recommendations for staging prostate cancer

Recommendations	Strength classification
Any risk group staging	
Use pre-biopsy MRI images to obtain local staging information	
Low-risk localized disease	
Do not use additional images for preparation purposes	
Intermediate risk disease	
For patients with International Society of Urological Pathology grade 3 disease, include at least cross-sectional abdominopelvic imaging and a bone scan for metastatic screening.	Weak
Perform PSMA PET/CT, if available, to increase accuracy.	Weak
High-risk localized disease/locally advanced disease	
Perform metastatic screening using PSMA PET/CT, if available, and at least cross-sectional abdominopelvic imaging and a bone scan.	Strong

CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen. Source: The Author.

Category T

The cT category depends on the DRE finding, but the increasing use of MRI and in particular T2-weighted imaging is driving stage migration. In 552 men treated by RP in seven different Dutch centres, MRI showed significantly higher sensitivity (51% vs 12%; $p < 0.001$) and lower specificity (82% vs 97%; $p < 0.001$) than DRE for non-organ confined disease. All risk groups redefined that using MRI findings instead of DRE findings showed better BCR-free survival due to improved discrimination and associated stage change (Soeterik et al., 2021).

Category N

Abdominal CT and MRI indirectly assess nodal invasion using lymph node (LN) diameter and morphology. Typically, LNs with a short axis of >8 mm in the pelvis and >10 mm outside the pelvis are suspicious for malignancy, with a sensitivity below 40%. Because CT and MRI lack sensitivity for direct detection of positive LNs, nomograms combining clinical and biopsy findings have been used to estimate the risk of patients harbouring positive LNs. PSMA PET/CT has good specificity for LN involvement. In a review and meta-analysis including 37 articles, a subgroup analysis was performed in patients who underwent PSMA PET/CT for primary staging. In a per-patient analysis, the sensitivity and specificity of 68Ga-PSMA PET were 77% and 97%, respectively, after extended LN dissection at the time of RP. In a lesion-based

analysis, sensitivity and specificity were 75% and 99%, respectively. In summary, PSMA PET/CT is more sensitive in N staging than MRI, abdominal contrast-enhanced CT, or choline PET/CT. However, small LN metastases, under the spatial resolution of PET, may still be missed (Perera et al., 2020).

Category M

Bone scan has been the most widely used method for evaluating bone metastases in PCa, with pooled sensitivity and specificity of 79% (95% CI: 73–83%) and 82% (95% CI: 78–85%), respectively, at the patient level. Whole-body diffusion-weighted and axial MRI are more sensitive than bone scans and targeted conventional radiography in detecting bone metastases in high-risk PCa. Whole-body MRI is also more sensitive and specific than combined bone scan, targeted radiography, and abdominopelvic CT. However, PSMA PET/CT appears to be the most accurate way to stage metastatic spread. In a prospective multicenter study of patients with high-risk PCa prior to curative surgery or RT (RT; proPSMA trial), 302 patients were randomly assigned to conventional imaging or Ga-PSMA-11 PET/CT. The primary outcome focused on the accuracy of first-line imaging for identifying pelvic LNs or distant metastases. The accuracy of Ga-PSMA PET/CT was 27% (95% CI: 23-31) higher than that of CT and bone scan (92% [95% CI: 88-95] vs 65% [95% CI: 60-69]; $p < 0.0001$). Conventional imaging had lower sensitivity (38% [95% CI: 24-52] vs 85% [95% CI: 74-96]) and specificity (91% [95% CI: 85-97] vs 98% [95% CI: 95-100]) than PSMA PET/CT. Furthermore, Ga-positron emission tomography (PSMA-PET/CT) led to treatment change more frequently than conventional imaging (41 [28%] men [95% CI: 21–36] vs 23 [15%] men [95% CI: 10–22], $p = 0.08$), with fewer equivocal findings (7% [95% CI: 4–13] vs 23% [95% CI: 17–31]) and lower radiation exposure (8.4 vs 19.2 mSv; $p < 0.001$). As a consequence, replacing bone scans and abdominopelvic CT with more sensitive imaging modalities may be a consideration in high-risk PCa patients undergoing initial staging (Hofman et al., 2020).

Assessment of life expectancy and health status

Assessment of life expectancy and health status is important in clinical decision-making about screening, diagnosis, and treatment of PCa. Country-specific life tables are available; however, survival should be individualized based on, for example, gait speed or using tools such as the Cumulative Illness Score Rating—Geriatrics (CISR-G), the Charlson Comorbidity Index (CCI), or the clinical frailty score. To assess the suitability of older adults for treatment, the panel suggests a systematic assessment of health status using the G8 screening tool as well as the Mini-COG. This may identify reversible health problems, which after treatment would facilitate alternative treatment options (Borson et al., 2003).

In localized disease, a life expectancy >10 years is considered mandatory for any survival benefit from local treatment. Increased comorbidity greatly increases the risk of dying from causes unrelated to PCa. In an analysis of 19,639 patients aged >65 years who did not receive curative treatment, most men with a CCI score $\geqslant 2$ died of concurrent causes within 10 years of follow-up, regardless of their age at diagnosis. Tumor aggressiveness had little impact on overall survival (OS), suggesting that patients could have been spared biopsy and cancer diagnosis. Men with a CCI score $\leqslant 1$ had a low risk of death within 10 years, especially for well- or moderately differentiated lesions. Patients with a life expectancy <10 years should undergo monitoring with

initiation of androgen deprivation to alleviate symptoms (watchful waiting) (Albertsen et al., 2011).

Conclusion

In this study, the comparison of new PCa screening strategies demonstrated that each method has distinct advantages and limitations. The results indicate that combining tests, such as PSA and MRI, can increase diagnostic accuracy and reduce false positives, providing more efficient and personalized screening. In addition, the implementation of liquid biopsies as a complementary tool may offer a less invasive approach with the potential for early detection.

The findings highlight the importance of adopting a multimodal approach to PCa screening, taking into account individual patient factors and costs associated with different methods. The adoption of these strategies can significantly improve clinical outcomes, reducing mortality and promoting a better quality of life for patients.

Finally, this study highlights the need for continued research to validate these strategies in different populations and clinical settings, aiming to optimize screening protocols and maximize public health benefits.

Abreviations

BCR - Biochemical recurrence, BCRFS - Biochemical recurrence-free survival rates, PCa - Prostate cancer, CCI - Charlson Comorbidity Index, CISR-G - Cumulative Illness Score Rating—Geriatrics, CSS - Cancer-specific survival, ED - Erectile dysfunction, DRE - Digital rectal examination, RCT - Randomized controlled trials, EPE - Extraprostatic extension, ERSPC - European Randomized Trial of Prostate Cancer Screening, GS - Gleason score, ISUP - International Society of Urological Pathology, LN - Lymph node morphology, mpMRI - Multiparametric magnetic resonance imaging, miTNM - Molecular imaging TNM classification, NND - Number needed to diagnose, PET - Positron emission tomography, PI-RADS - Prostate Imaging Reporting and Data System, PSA - Prostate antigen Specific, PSMA - Prostate Specific Membrane Antigen, MRI - Magnetic Resonance Imaging, RP - Radical Prostatectomy, RS - Systematic Review, SDI - Sociodemographic Index, SG - Overall Survival, CT - Computed Tomography, TNM - Tumor, Node and Metastasis, TRUS - Transrectal Ultrasound, QV - Quality of Life.

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