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Brief Report

Editorial by Armando Stabile, Tobias Nordström on pp. 245–246 of this issue

Prostate Cancer Detection in Younger Men: A Comparative Analysis of Systematic and Magnetic Resonance Imaging–targeted Biopsy in the PROBASE Trial

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Abstract

The optimal approach for prostate cancer (PC) screening, including the ideal starting age and most effective diagnostic method, remains under investigation. We evaluated the diagnostic performance of magnetic resonance imaging (MRI)-targeted biopsy (TBx) and systematic biopsy (SBx) in detecting clinically significant PC (csPC) in men aged 45–50 yr in PROBASE, a prospective, randomized trial of a risk-adapted screening strategy. A total of 525 participants with elevated prostate-specific antigen (≥3 ng/ml) underwent MRI followed by biopsy. Of the 209 PC cases detected, 148 (71%) were csPC. SBx identified 94% of csPC cases, while TBx detected 74% ($p \leq 0.05$). SBx also diagnosed significantly more low-grade PCs than TBx ($p < 0.001$). These findings suggest that relying solely on MRI-TBx may lead to underdiagnosis of csPC. Combining SBx with TBx remains the most effective strategy for early detection of PC in young men undergoing screening. Future research should explore optimization strategies to reduce unnecessary

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Ultrasound;
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biopsies while maintaining high detection rates for csPC.

This trial is registered on the ISRCTN registry as ISRCTN37591328 (https://www.isrctn.com/ISRCTN37591328). The study protocol can be accessed at https://doi.org/10.1016/j.eururo.2013.05.022.

ADVANCING PRACTICE

What does this study add?

This study provides the first population-based insights into screening based on prostate-specific antigen and magnetic resonance imaging (MRI) for men aged 45–55 yr. It demonstrates that systematic biopsy remains essential, detecting 94% of clinically significant prostate cancers, whereas MRI-targeted biopsy alone missed 26% of these cases. The findings highlight the challenges of MRI interpretation in younger patients and emphasize the need for a combined biopsy approach in this setting.

Clinical Relevance

Prostate cancer screening is experiencing a revival — particularly in Europe — with the recent launch of several population-based organized testing programmes. Key aspects, such as the age at screening initiation, diagnostic pathways, and treatment strategies in the event of positive results, are under intense examination. Current data from the German PROBASE study, where men begin screening at age 45 and follow a PSA-triaged, MRI-based pathway, highlight the importance of combining systematic and targeted prostate biopsy sampling to detect ISUP Grade Group 2 or higher cancers. These findings stand in sharp contrast to results from the Swedish GÖTEBORG-2 trial, where random biopsies led to an increased detection of indolent tumours. Differences in demographics, baseline prostate cancer risk, and possibly MRI interpretation and quality may help explain this discrepancy. The search for the optimal screening strategy for 2025 and beyond continues, along with the challenge of defining which clinically important cancers must not be overlooked. Associate Editor: Gianluca Giannarini, MD.

Patient Summary

We looked at different prostate biopsy methods as part of a prostate cancer screening trial for men aged 45–50 years. Our findings show that using targeted biopsy guided by MRI (magnetic resonance imaging) may miss aggressive cancers. A combination of systematic and targeted biopsies may be necessary for accurate detection.

It has been shown that prostate cancer (PC) screening using prostate-specific antigen (PSA) testing followed by systematic biopsy (SBx) reduces PC-related mortality but carries the risk of overdiagnosis and unnecessary biopsies [1–3]. Multiparametric magnetic resonance imaging (mpMRI) has emerged as an essential diagnostic tool that allows MRI-targeted biopsy (TBx) of suspicious lesions (Prostate Imaging-Reporting and Data System [PI-RADS] scores 4–5) [4,5]. Current guidelines recommend MRI before biopsy, but its role in a primary screening setting remains under investigation, particularly in younger men, in whom MRI interpretation is challenging and highly dependent on reader experience [6]. The PROBASE trial is evaluating PC detection in men aged 45–50 yr using SBx, TBx, and a combined (SBx + TBx) approach.

PROBASE is a prospective randomized screening trial involving 46 495 men aged 45 yr at enrollment. Participants with PSA $\geq$3 ng/ml underwent mpMRI, followed by TBx and SBx. Biopsies were conducted transrectally or transperineally using software-assisted fusion techniques, with histopathology centrally reviewed by an experienced pathologist. For TBx, a maximum of three lesions were identified and two cores were biopsied from each lesion. For SBx, a scheme according to the size of the prostate was used, which comprised 12 independent systematic cores in most cases. This present analysis includes data from 525 participants who underwent primary biopsy between February 2014 and September 2023 (Supplementary Table 1). The primary outcome was the detection rate for clinically significant PC (csPC; International Society of Urological Pathology grade group [GG] $\geq$2). Secondary outcomes included the detection rates of low-grade PC (GG 1) and false-negative rates for both TBx and SBx.

The final study cohort consisted of 525 participants who underwent TBx and SBx after detection of elevated PSA at screening. Among these men, 209 PCs were diagnosed (39%), of which 148 (71%) were classified as csPC. SBx detected 94% (139/148) of csPC cases, significantly outperforming TBx, which detected 74% (109/148). SBx identified 26% (39/148) of csPC cases that TBx missed, whereas TBx detected 6% (9/148) of csPC cases not identified by SBx. Comparison of the biopsy strategies using the McNemar test revealed that SBx detected significantly more csPC cases

($p \leq 0.05$). For GG 1 cancers, SBx also detected more tumors (51/61, 84%) than TBx did (26/61, 43%; $p \leq 0.001$; Table 1).

A total of 17/209 tumors (8.1%) were scored as PI-RADS 1–2 on MRI, including 13 csPCs. Overall, MRI detected 91% (135/148) of csPC cases and 93% (57/61) of low-risk PC cases, and classified 19% (61/316) of subjects with negative biopsy findings as most likely to have no PC. The calculation was based on a cutoff of PI-RADS 3 for the biopsy decision (Table 2).

For men aged ≥50 yr, PC screening using an MRI pathway with or without additional biomarkers (kallikreins, Stockholm-3 test) with TBx alone has proven to be effective [7,8]. However, there are only sparse data on the MRI pathway for men aged 45–55 yr, which is the age group for which possible future PC screening programs are supposed to start according to current guidelines and the PRAISE-U project (www.praise-u.eu). Our findings suggest that for younger men, SBx remains a critical component of PC detection, as TBx alone misses a significant proportion of csPC cases. The better performance of SBx in this cohort is probably influenced by prostate size, with a smaller prostate volume in younger men allowing more effective systematic sampling. A closer look at the cases that were missed on SBx revealed two reasons: (1) unfavorable tumor location and (2) small tumors. In terms of tumor location, we especially observed discrepancies for anterior, apical, and lateral lesions, which are often more difficult to reach via transrectal access. In our cohort, a considerable proportion of examinations had PI-RADS 3 findings. Owing to the often-diffuse signal changes in the T2-weighted sequences and diffusion with widespread perfusion enhancement, tumor detection on MRI is more challenging in younger men [9].

Despite the advantages of MRI-based screening, its widespread use is limited by costs and infrastructure demands. The PROBASE data suggest that avoiding SBx would lead to missed diagnosis in 26% of csPC cases, reinforcing the importance of a combined TBx and SBx approach. Notably, the Göteborg study reported a 50% reduction in overdiagnosis when SBx was omitted [2]. However, in the PROBASE cohort, only 29% of cancers detected were ISUP 1, which is lower than the rate in the Göteborg cohort, and both TBx and SBx yielded one additional csPC case for every ISUP 1 PC detected. Given the uncertainty regarding the long-term progression of low-grade PC in young patients, overdiagnosis should be interpreted with caution [10].

Our study also highlights the limitations of MRI reading for younger men, for whom false-negative rates remain a concern [11]. In 31 cases, MRI failed to identify a lesion that was subsequently diagnosed via biopsy, including 14 cases of csPC. The use of artificial intelligence (AI)-assisted MRI interpretation could improve the accuracy of detection, which will be the subject of future PROBASE investigations. In addition, biopsy techniques and fusion technologies should be continuously refined to minimize the likelihood of sampling errors. Quality control measures, including certification of biopsy centers and standardized reporting akin to the Prostate Imaging-Quality (PI-QUAL) system for MRI, could enhance the reliability of TBx.

Several study limitations must be considered. First, PROBASE was designed before mpMRI was integrated into PC

Table 1 – Cancer detection via targeted and systematic biopsy for all cancers and clinically significant cancers

Detection	Cancers detected, *n* (%)	
	All cancers[a]	Clinically significant[b]
Overall	209	148
Detected via systematic + targeted biopsy	116 (56)	100 (68)
Detected via systematic biopsy only	74 (35)	39 (26)
Detected via targeted biopsy only	19 (9.1)	9 (6.1)
Totals by biopsy type		
Total via systematic biopsy[c]	190 (91)	139 (94)
Total via targeted biopsy[d]	135 (65)	109 (74)

GG = International Society of Urological Pathology group grade.
[a] Prostate cancers of GG 1–5 according to the maximum grade group between systematic and targeted biopsies.
[b] Prostate cancers of GG 2–5 according to the maximum grade group between systematic and targeted biopsies.
[c] Detected via systematic + targeted biopsy, or systematic biopsy alone.
[d] Detected via targeted + systematic biopsy, or targeted biopsy alone.

Table 2 – Distribution of PI-RADS scores for the positive and negative biopsies

Biopsy result	PI-RADS score, *n* (%)				Total
	1 or 2	3	4	5	(*n*)
Negative	61 (78)	179 (74)	70 (39)	6 (23)	316
Positive					
Total	17	63	109	20	209
GG 1	4 (5.1)	31 (13)	23 (13)	3 (12)	61
GG 2–5	13 (17)	32 (13)	86 (48)	17 (65)	148
Total	78 (100)	242 (100)	179 (100)	26 (100)	525

GG = International Society of Urological Pathology grade group; PI-RADS = Prostate Imaging-Reporting and Data System.

screening guidelines, and MRI was only performed for PSA ≥3 ng/ml, limiting its impact on screening decisions. MRI quality and reader experience varied across the study sites, which reflects real-world variability but could potentially have influenced TBx performance. In addition, the use of different biopsy approaches (transrectal vs transperineal) across sites may have affected detection rates, although both methods are well established in clinical practice. A sample size of 525 patients might not be representative, and larger cohorts must be analyzed to reach reliable conclusions. Finally, the study findings are limited to younger men and may not be generalizable to older populations undergoing PC screening.

In conclusion, SBx remains essential for PC detection in younger men and identifies a significantly higher proportion of csPC cases than TBx alone. While MRI-TBx reduces overdiagnosis and unnecessary procedures, it is insufficient as a standalone method in this population. A combined SBx + TBx approach ensures optimal PC detection while balancing the risks of overtreatment and missed diagnoses. Future research should focus on optimizing MRI interpretation, incorporating AI-assisted tools, and refining biopsy techniques to further improve early PC detection.

Author contributions: Matthias Boschheidgen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2025.05.020.

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