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RESEARCH LETTER

# 2023/2024 update of the national prostate cancer guidelines in Sweden

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The prostate cancer (PCa) landscape is rapidly changing, encompassing improvements in diagnostics – including screening, hereditary risk management, organized prostate cancer testing (OPT), biopsy techniques, and assessment of bone metastases – as well as treatments, including new approaches for metastatic disease. Consequently, the Swedish National Prostate Cancer Guidelines is now updated annually, sometimes even with interim updates throughout the year. The most important changes in the guidelines since the last publication in 2022 [1, 2] are summarized in this article.

The criteria for hereditary PCa risk now include mutations in the cancer-associated genes MSH2, MSH6, and TP53, in addition to BRCA2 and HOXB13. Testing for BRCA2 mutations is recommended for men under 60 diagnosed with metastatic PCa, or with Gleason pattern 5, that is ISUP grade 5, and/or a family history of related cancers, along with other genes where hereditary cancer syndromes are suspected.

The guidelines now explicitly state that in primary care a digital rectal examination (DRE) should precede a referral for PCa assessment. DRE findings should be documented in the referral, and a repeat prostate specific antigen (PSA) test should be conducted if PSA is between 3 and 10 µg/L. Men with normal DRE and a repeat PSA < 3 µg/L, or a negative MRI (PI-RADS 1–2) and PSA density (PSAD) < 0.20 µg/L/cm$^3$, or a PI-RADS 3 with a PSAD < 0.10 µg/L/cm$^3$ can be referred back to primary care for follow-up. For men with PI-RADS 3 and PSAD of 0.10–0.199 µg/L/cm$^3$, and for all men with PI-RADS 4–5, only targeted biopsies are recommended. Systematic biopsies are recommended primarily for PI-RADS 1–3 and PSAD ≥ 0.20 µg/L/cm$^3$ (Table 1). To reduce the risk of infection, povidone-iodine and antibiotic prophylaxis with risk-based adjustment should always be used for transrectal (TR) biopsies. Transperineal (TP) biopsies are recommended as an alternative with a lower risk of infection.

TP biopsies should be labelled according to the same system as used for TR biopsies, with biopsies stored in separate containers labelled by sector. Guidance on reporting intraductal carcinoma findings, given their negative prognostic significance, has been refined. A standardized reporting template for PSMA-PET/CT use is also recommended to support consistency in imaging-based diagnostics. Use of free-to-total PSA ratio is no longer recommended, as PSA density alone is deemed sufficient.

There are several supplementary tests that can guide the decision-making process regarding prostate biopsies. However, the evidence is insufficient to support their cost-effectiveness as an addition to MRI-based diagnostics. Therefore, none of these tests are recommended for routine clinical use.

Due to large prognostic differences within the intermediate-risk group, this group is now subdivided into 'favourable' and 'unfavourable' intermediate risk.

For active surveillance, the follow-up protocol has been clarified, emphasizing that PSAD, PI-RADS, and the size of the index lesion at diagnosis are the strongest predictors of progression. Additionally, the PRECISE criteria are recommended to quantify changes over time on MRI. Biopsies may be avoided for PI-RADS 3–5 if a new MRI shows PRECISE 2–3, PSAD < 0.15 µg/L/cm$^3$, and an increase of < 0.05 µg/mL/cm$^3$ since previous imaging [3].

Recommendations on fractionation for men with high-risk cancer now include the option of treating the seminal vesicles [4]. Pelvic lymph node irradiation can also be considered in selected men at high risk for lymph node metastases [5]. After radical prostatectomy, men with an ISUP grade < 4 and a PSA doubling time > 12 months have a low risk of progression to metastasis and death by PCa. Salvage treatment may therefore cause more harm than benefit, and caution is therefore advised when considering this.

For older men, detailed assessment tools beyond the ECOG scale, such as Geriatric-8 and Minicog, are recommended to support treatment decisions, particularly for metastatic PCa and castration-resistant PCa (CRPC). Following the publication of the first guidelines for cardio-oncology by the European Society of Cardiology, the risk of cardiovascular disease (CVD) associated with androgen deprivation therapy (ADT) has been further highlighted [6]. Men with high risk of CVD or diabetes should

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**Table 1.** Recommendations on when and how to take biopsies (targeted and/or systematic) at different PI-RADS levels and PSA-density.

| MRI PI-RADS Score | PSA-density g/L/cm$^3$ | | |
|---|---|---|---|
| | < 0.10 | 0.10–0.199 | ≥ 0.20 |
| PI-RADS 1–2 | No biopsy | No biopsy | Biopsy (S) |
| PI-RADS 3 | No biopsy | Biopsy (T) | Biopsy (T + S) |
| PI-RADS 4–5 | Biopsy (T) | Biopsy (T) | Biopsy (T) |

T, Targeted biopsies; S, Systematic biopsies.

be referred to primary care for optimization of medications. GnRH antagonists are recommended as ADT for men with high risk of CVD.

For men in good health who have oligometastatic PCa, unsuitable for radiotherapy and not candidates for triple therapy, treatment options now include ADT combined with abiraterone, apalutamide, enzalutamide, or docetaxel.

Poly-ADP ribose polymerase inhibitors (PARP-inhibitors), a class of targeted drugs that work by taking advantage of the impaired DNA repair mechanisms in some cancer cells, are recommended for men with BRCA1/2 mutations for whom chemotherapy is not indicated [7]. To determine eligibility for treatment with PARP-inhibitors, an analysis of BRCA mutations in tumor tissue (somatic and germline) or circulating tumor DNA (ctDNA) or a blood sample for germline mutation analysis is required. For predictive testing of treatment efficacy, tissue testing or ctDNA analysis is preferred, as examining only germline mutations may overlook any somatic mutations. Analysis of bone lesions is less suitable due to the impact of decalcification protocols on DNA quality. ctDNA can detect mutations in solid tumors with high sensitivity [8]. Advantages of ctDNA analysis include shorter processing time, detection of both somatic and germline mutations, and no need for a tissue sample. However, in men with low tumor burden or minimal disease activity, sensitivity may be lower due to low ctDNA levels, so it is recommended that samples for analysis be taken during progressive disease.

For transgender women treated with estrogen, ensuing prostate atrophy and decrease in PSA must be considered when considering screening. Given the complex considerations involved in managing care for these individuals, limited research in the area, and the potentially increasing number of affected individuals, each healthcare region is advised to assign a urologist to manage PCa diagnostics and treatment for transwomen. A first workshop to start this work is planned by Regional Cancer Centres (RCC) in Sweden in February 2025.

In conclusion, these updates of the national guidelines for PCa in Sweden offer a more nuanced, evidence-based, and patient-centered approach to PCa management, including aspects of prevention, diagnostics, treatment, and support across the full disease spectrum.

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