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The Swedish national guidelines on prostate cancer, part 1: early detection, diagnostics, staging, patient support and primary management of non-metastatic disease

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ABSTRACT

Objective: There is now an unprecedented amount of evidence to consider when revising prostate cancer guidelines. We believe that there is a value in publishing summaries of national clinical guidelines in English for others to read and comment on.

Methods: This is part 1 of a summary of the Swedish prostate cancer guidelines that were published in June 2022. It covers the early detection, diagnostics, staging, patient support and management of the non-metastatic disease. Part 2 covers recurrence after local treatment and management of the metastatic disease.

Results: The 2022 Swedish guidelines include several new recommendations: rectal iodine-povidone to reduce post-biopsy infections, external beam radiation with focal boost to the tumour, use of a pre-rectal spacer to reduce rectal side effects after external beam radiotherapy in some expert centres, 6 months' concomitant and adjuvant rather than neoadjuvant and concomitant hormonal treatment together with radiotherapy for unfavourable intermediate and high-risk disease, and adjuvant abirater-one plus prednisolone together with a GnRH agonist for a subgroup of men with very high-risk disease. The Swedish guidelines differ from the European by having more restrictive recommendations regarding genetic testing and pelvic lymph node dissection, the risk group classification, recommending ultra-hypofractionated (7 fractions) external radiotherapy for intermediate and selected high-risk cancers, by not recommending any hormonal treatment together with radiotherapy for favourable intermediate-risk disease, and by recommending bicalutamide monotherapy instead of a GnRH agonist for some patient groups.

Conclusions: The 2022 Swedish prostate cancer guidelines include several new recommendations and some that differ from the European guidelines.

ARTICLE HISTORY

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KEYWORDS Prostate cancer; guideline; diagnosis; staging; patient support; treatment

1. Introduction

In the past few years, a large number of important randomized clinical prostate cancer trials have been published. There is now an unprecedented amount of evidence for clinical guidelines groups to consider when revising national and international guidelines. Although the same evidence from clinical trials and other studies are available for all guideline groups, the clinical conclusions drawn from the evidence may differ – not only because the health care systems and the populations differ between countries, but also because the clinical interpretation of crude scientific data is subjective. We believe that there is a value in publishing summaries of national clinical guidelines in English for others to read and possibly comment on.

This is part 1 of 2 of a summary of the most recent version of the Swedish prostate cancer guidelines, published in June 2022. This article covers the early detection, diagnostics, staging, patient support and primary management of the non-metastatic disease. Recurrence after local treatment with curative intent and management of men with metastatic disease are covered in part 2 [1]. The summary focuses on new recommendations, based on recently published pivotal clinical trials, and on recommendations that differ from the European guidelines [2].

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2. The national prostate cancer guidelines group

The first Swedish national prostate cancer guidelines were published in 2014. They have been annually revised since then. A draft is publicly available online and sent for comments to various organisations. When the comments have been considered by the guidelines group and the appropriate revisions have been made, the final version is approved by the Swedish Confederation of Regional Cancer Centres before publication.

Each of the 6 regional cancer centres appoints one oncologist and one urologist to the guidelines group. The group and its associated experts also include cancer nurse specialists, radiologists, a pathologist, a nuclear medicine specialist, a hospital social worker, a sexologist, a clinical chemist, a general practitioner, a clinical geneticist, patient representatives and an administrative co-ordinator.

The guidelines group closely co-operates with the National Prostate Cancer Register of Sweden (NPCR). NPCR data (publicly available in English at npcr.se) are used to evaluate the influence of the national guidelines on clinical care [3,4]. Hospital-level outcomes of specific quality indicators are regularly reported to all heads of urology and oncology departments in Sweden [5].

3. Epidemiology

Prostate cancer is the most common cancer in Sweden. With approximately 11,000 new cases per year in a population of 10.4 million people, Sweden has the third highest age-standardized incidence in Europe [6]. The pandemic caused an incidence drop to 8,900 in 2020 [7]. In the past 20 years, agestandardized mortality has decreased by a third (Figure 1). Among men under 80 years of age the mortality has almost halved, probably both because of earlier detection leading to more men being cured by surgery and local radiotherapy, and because of more effective treatment of metastatic disease.

4. Early detection and screening

The Swedish National Board of Health and Welfare, in agreement with other national healthcare authorities, recommend against population-based prostate cancer screening because of the associated issues with overdiagnosis and overtreatment. The Board does, however, acknowledge that individual men may consider the potential benefits and harms of PSA testing differently. The national guidelines recommend that men be informed about the potential consequences, and offered testing if they after proper information wish to. A national brochure about PSA testing is available online and in general practice.

In 2018, the Swedish Ministry of Health and Social Affairs commissioned the Confederation of Regional Cancer Centres to do something about the widespread, ineffective, unorganized PSA testing. The Confederation proposed regional, population-based, developmental projects with "organized prostate cancer testing" (OPT) aiming at improving pre-testing information, reducing socioeconomic inequality, making the testing and subsequent diagnostics more effective, and gaining knowledge and experience to prepare for a future national screening programme [8]. The regional projects, of which 5 are ongoing and 10 are planned to start in 2022 or 2023 (Sweden has 21 regions), involve letters with a brief description of the pros and cons of prostate cancer testing. In-depth information is available online. Men who opt for testing are managed according to a strict algorithm in a separate pathway outside routine health care, in essence just like in a formal screening programme. Birth cohorts of men are gradually invited with the aim of including the entire target population of men between 50 and 74 years of age within 7-9 years. All data

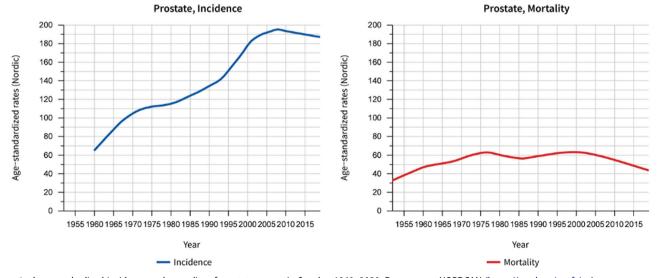


Figure 1. Age-standardized incidence and mortality of prostate cancer in Sweden 1960–2020. Data source: NORDCAN (https://nordcan.iarc.fr/en).

are registered in regional databases for quality control, development and research.

4.1. Hereditary risk group and genetic testing

Family history is one of the strongest risk factors for prostate cancer [9]. Men with two affected first-degree relatives are recommended PSA testing from the age of 40 years, with shorter intervals and a lower cut-off ($2 \mu g/l$) for urology referral than men in general.

Prostate cancer may be the one among common cancers for which inherited predisposition is most important [10], but germline testing for high penetrance germline mutations has only recently become clinically important. BRCA2 and HOXB13 have emerged as the two clinically most important prostate cancer predisposition genes [11,12]. Men with deleterious BRCA2 or HOXB13 mutations are recommended the same follow-up as men with a strong family history of prostate cancer.

By 2020 the Swedish guidelines recommend that men younger than 60 years with metastatic or Gleason pattern 5 prostate cancer and a first-degree relative with BRCA2-associated cancer should be offered onco-genetic counselling about BRCA2 mutation testing. So should men with a family history suggesting Lynch syndrome. The reason for being more restrictive with genetic testing than the European guidelines [2] is the lack of population-based studies of the practical consequences for the tested men and their families. A Swedish working group is preparing for how more extensive testing is best implemented in routine clinical care.

5. Diagnosing prostate cancer

Standardised cancer diagnostic pathways were implemented in Swedish healthcare in 2015, inspired by Danish and Norwegian examples. The prostate cancer pathway inclusion criteria are a palpable prostate nodule and/or a serum PSA value of $3 \mu g/l$ for men younger than 70 years, $\geq 5 \mu g/l$ for men aged 70–80 years and $\geq 7 \mu g/l$ for men older than 80 years. The pathway specifies procedures and optimal time frames for diagnostics and staging. Sadly, the standardised pathway has not much reduced the national average waiting times for prostate cancer patients; less than half of them are managed within the optimal time frames. By 2020, the guidelines recommend an MRI as the first investigation for men with a raised PSA value, except for men with PSA $\geq 100 \,\mu$ g/l, verified metastasis or a short life expectancy. Whether the biopsy protocol should primarily aim at maximising the detection of Gleason score 7–10 cancer or at reducing the detection of Gleason score 6 cancer is debated. The Swedish guidelines group leans towards the latter: men with a benign DRE, a non-suspicious MRI (PI-RADS 1–3) and a PSA density <0.15 μ g/l/cm³ are not routinely recommended a prostate biopsy. Targeted biopsies only are recommended for most men with a PI-RADS 4–5 lesion. The locations of the biopsies are described according to a national template (Figure 2).

Because of the low prevalence of fluoroquinolone-resistant bacteria in Sweden, the guidelines recommend a single dose of ciprofloxacin as standard prophylaxis before prostate biopsy. A recent meta-analysis suggests that rectal cleansing with povidone-iodine reduces infectious complications after transrectal prostate biopsy [13]. The European guidelines since 2021 recommend rectal povidone-iodine cleansing and the Swedish guidelines now also do so. Another way to reduce post-biopsy infection is using the transperineal route. Transperineal prostate biopsy is in Sweden routinely done only at a few centres, but the 2022 guidelines stress the importance of implementing the transperineal biopsy technique to reduce the risk of postbiopsy infection.

Many bloods, urine and tissue tests predict the likelihood of Gleason score 7–10 cancer on biopsy in men with raised PSA values [14]. Using these tests as "a filter" substantially reduces the number of prostate biopsies and diagnosed Gleason score 6 cancers. The Stockholm3 test, combining serum and genetic markers with clinical information [15,16], has recently been evaluated for an MRI-based diagnostic pathway in a screening-like setting [17]. The guidelines support using the Stockholm3 test in regional projects with organized prostate cancer testing to gain evidence for its performance in repeated testing.

6. Staging

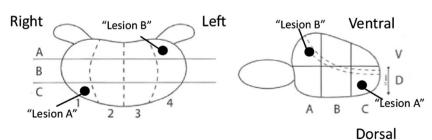


Figure 2. The Swedish national template for describing the localisation of prostate biopsies. In this example, the locations are described as C1D (Lesion A) and A4V (Lesion B).

The Swedish risk group classification is based on the D'Amico classification [18], Cambridge Prognostic Groups [19], NPCR data [20] and considerations on how targeted biopsies and

MRI results affect the prognostic value of the risk group categorisation (Box 1, Figure 3). The Swedish Likert scales for describing the probability of extra-prostatic tumour extension (EPE) and seminal vesicle invasion (SVI) are described in Box 2.

The Swedish prostate cancer risk group classification				
1	Very low risk	T1c, a total of \leq 8 mm Gleason score 6 cancer in \leq 4 of 8–12 systematic biopsy cores, PSA <10 µg/l and PSA density $<$ 0.15 µg/l/cm ³		
2	Other low risk	T1–T2a, Gleason score 6 and PSA <10 μg/l, but not very low risk		
3	Intermediate risk	T2b–T2c and/or Gleason score 7 and/or PSA 10–19 μg/l		
4	High risk	T3 on DRE or EPE/SVI 5 on MRI or Gleason score 8 or Gleason score 4 + 3 = 7 in ≥50% of systematic biopsy cores or in targeted biopsies from a PI- RADS 5 lesion or PSA 20-49 μq/I		
5	Very high risk	Two or more of the high-risk criteria T3/GS 8/PSA 20-49 µg/l or T4 and/or Gleason score 9-10 and/or PSA ≥50 µg/l		

ation, EPE: extra-prostatic extension, SVI: seminal vesicel invasion.

prostatic tumour extensior	rt scale for describing the probability of extra- n (EPE) on MRI. A similar scale is used for sem- (SVI). Created by Fredrik Jäderling,
1 Very low risk of EPE	No contact between tumour and capsule on MRI
2 Low risk of EPE	<12 mm tumour contact capsule and no signs of EPE
3 Intermediate risk of EPE	≥12 mm tumour contact capsule but no signs of EPE
4 High risk of EPE	≥12 mm tumour contact capsule and indirect signs of EPE
5 Very high risk of EPE	Measurable radial tumour component outside capsule

CT and MRI both have low sensitivity and specificity for N-staging [21]. Only 4% of men with Cambridge Prognostic Group 4 have findings suggesting lymph node metastasis on CT/MRI [22]. For this reason and because suspicion of N1 often does not affect the treatment choice, abdominal CT or MRI is not recommended for patients with Cambridge Prognostic Group 4 cancer unless the PSA is >50 ng/ml. A bone scan with SPECT-CT or an MRI of the axial skeleton is recommended for M-staging for those with high or very high-risk diseases. Although PSMA-PET-CT has higher sensitivity to detect metastasis [23], there is no evidence for how limited metastatic findings on PSMA-PET-CT should affect treatment. Therefore, and because of limited PET resources, the guidelines recommend PSMA-PET-CT as optional rather than as the method of choice for staging.

7. Patient support, the treatment decision and rehabilitation

The 2009 Swedish national cancer strategy stated that every cancer patient should be offered a personal cancer nurse specialist for psychosocial support and for help with coordinating their care. The cancer nurse specialist should shortly after the notification of the diagnosis do a basic needs assessment and provide the patient with written, individualized, care and rehabilitation plans. For special needs, the patient should be offered contact with a social counsellor, urotherapist, sexologist, physiotherapist, dietitian, etc.

It is the responsibility of the diagnosing urologist and the cancer nurse specialist to ensure that the patient has been provided with sufficient verbal and written information to be able to take an active role in the treatment decision. The national guidelines' appendix includes patient information sheets about the different treatments for nonmetastatic disease, advice on self-management (physical exercise, smoking cessation, etc), sexual side-effects and their management, and hormonal treatment (methods and management of side-effects). Patients considered for either radical prostatectomy or primary radiotherapy should be offered appointments with both a prostate cancer surgeon and a radiation oncologist. Before these appointments, a structured assessment of their urinary, bowel and sexual functions should be carried out, as these may affect the risk of treatment side effects. All patients should be informed about their right to have a second opinion at another centre.

The guidelines specify clinical situations when the management should be discussed at a multidisciplinary team conference, such as high or very high-risk non-metastatic disease, metastatic disease, biochemical recurrence after surgery or primary radiotherapy, progressive castration-resistant disease, and co-morbid conditions that make the treatment choice particularly difficult.

All centres providing radical prostatectomy or radiotherapy should provide structured rehabilitation programmes for restoring the patients' sexual, urinary and bowel functions. The guidelines include specific recommendations about managing side effects such as erectile dysfunction, urinary incontinence, strictures, radiation cystitis, radiation proctitis, lymphoedema, osteoporosis and hot flashes.

8. Active surveillance and watchful waiting

Active surveillance is defined as expectant management including repeated diagnostic investigations with the aim of offering curative treatment in case of early signs of progression, whereas watchful waiting involves PSA testing and digital rectal examination with the aim of starting hormonal treatment in case of progression to locally advanced or metastatic disease.

Active surveillance reduces overtreatment and is associated with better quality of life than radical

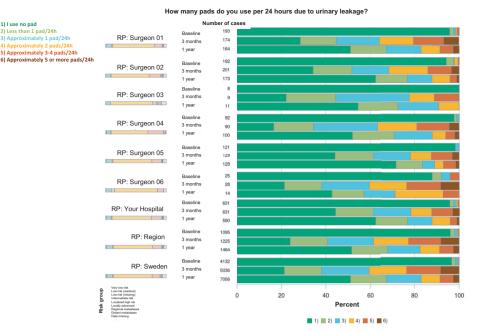


Figure 3. The view of the patient-reported outcome measures after radical prostatectomy collected by the National Prostate Cancer Register of Sweden is available online for all operating departments for quality control and improvement.

prostatectomy and radiotherapy [24], and has become the dominant management for low-risk prostate cancer in Sweden. In 2018–2020 almost all men under 80 years with a very low (93%) or low (84%) risk of the disease started active surveillance (data online at npcr.se). Those with an intermediate risk of cancer are encouraged to take part in the SPCG-17 trial, which is evaluating the safety of an MRI-based follow-up with defined triggers for intervention [25].

The use of MRI and targeted plus systematic biopsies is paramount for the proper selection of men for active surveillance [26], but the evidence for an entirely MRIbased follow-up is not convincing [27]. The recommended active surveillance follow-up is a PSA test every sixth months, palpation annually, and, as a rule, a repeat biopsy every second to third year. Omitting repeat biopsies is acceptable in patients with low-risk disease who have had a recent unsuspicious MRI and has a stable PSA level with a density below 0.15 ng/l/cm³. The long-term safety of active surveillance depends on adherence to the follow-up protocol, but only 42% of active surveillance patients in Stockholm had in 2008 to 2017 the recommended repeat biopsy within one year, although the proportion increased in the later part of the studied time period [28].

Most patients on watchful waiting are old or have severe comorbidity. Although most elderly men with a localised low or intermediate-risk prostate cancer die from other causes than their prostate cancer, local tumour progression and metastatic disease may rapidly occur more than 15 years after diagnosis [29]. Active follow-up is therefore essential to detect progression early enough to start hormonal treatment, with or without local radiotherapy, in time to prevent severe symptoms and possibly also death from prostate cancer.

9. Radical prostatectomy

In Sweden, almost all radical prostatectomies are done laparoscopically with robot assistance (93% in 2021). Because high surgeon and hospital volumes are associated with better functional and oncological outcomes [30–32], the Swedish guidelines recommend that radical prostatectomy be done only by surgeons who do at least 25 procedures per year at departments with at least two such surgeons. As outcomes vary considerably also between high-volume surgeons [32], patient-reported outcome measures (PROMs) should systematically be collected with the NPCR's online questionnaire to facilitate continuous quality control. The heads of the departments have access to their own individual surgeons' results (Figure 3), as well as aggregated results on departmental, regional and national levels.

Extended pelvic lymph node dissection (ePLND) gives prognostic information and may guide postoperative radiotherapy, but is unlikely to be of therapeutic value [33] and increases the risk of postoperative complications [34,35]. The Swedish guidelines group draws a different conclusion from the evidence than the European guidelines [2] and does not recommend routine PLND, not even for patients with highrisk disease, partially because postoperative radiotherapy can now be guided by PSMA-PET/CT.

10. Radiotherapy: primary and adjuvant

Recent research and technical developments have led to a wide spectrum of different ways to deliver radiation treatment with curative intent. These are briefly described below. Specific treatment recommendations based on risk grouping are summarized in Box 3. Swedish national register data for the use of different radiotherapy modalities in 2021 are shown in Figure 4.

	MR
Box 3. Summary of recommended radiotherapy modalities and combina- tions with doses and fractionation for different risk groups. Please see	ima
Box 1 for definitions of the risk groups. Abbreviations: EBRT: external	me
beam radiation therapy, Gy: Gray, fx: fraction, HDR: high dose-rate, BT: brachytherapy, MRI: magnetic resonance imaging.	(IM
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Intermediate risk: First choice: Ultra-hypofractionated EBRT (6.1 Gy/7fx)	pat
Moderately hypofractionated EBRT (3 Gy/20fx) may be considered	[36
HDR-BT monotherapy (13–14Gy/2fx) may be considered, particularly when	eith
EBRT or surgery is not suitable (e.g. for patients with an ileoa- nal reservoir).	Gra
High risk	CH
EBRT with HDR-BT boost: EBRT (2 Gy/25fx or 3 Gy/13–14fx) + HDR-BT	the
(10 Gy/2fx or 14–15Gy/1fx)	nat
Moderately (3 Gy/20–22fx) or ultra-hypofractionated EBRT (6.1 Gy/7fx) when HDR-BT is not suitable	rad
EBRT with focal boost (2.2Gy/35fx to whole prostate + up to total 95 Gy	Sw
to tumour) may be considered.	are
Very high risk	ultı
EBRT with HDR-BT boost: EBRT (2 Gy/25fx or 3 Gy/13–14fx) + HDR-BT (10 Gy/2fx or 14 15 Gy/1fx)	far
(10 Gy/2fx or 14–15Gy/1fx). EBRT with focal boost (2.2Gy/35fx to whole prostate $+$ up to total 95 Gy	oth
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EBRT (2 Gy/39fx) in patients not eligible for combination therapy or focal boost	inte
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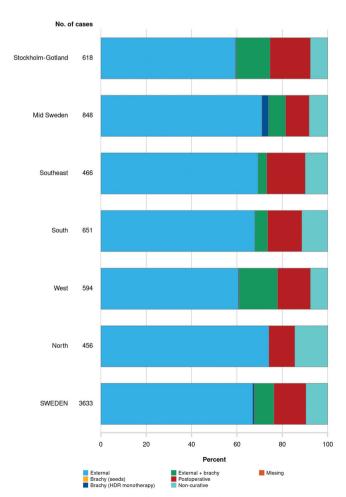


Figure 4. National register data from the National Prostate Cancer Register of Sweden for the use of different radiotherapy modalities in 2021 (npcr.se).

10.1. External beam radiotherapy (EBRT)

RI-based dose-planning with the use of fiducial markers for age-guided RT (IGRT) with volumetric arc radiation treatent (VMAT) or intensity-modulated radiation treatment MRT) techniques are recommended as standard of care. sing a pre-rectal hydrogel spacer should be considered in tients with an increased risk of significant rectal toxicity 6]. Recommended doses for EBRT with curative intent are ther 78 Gray in 39 fractions (conventional fractionation), 66 ay in 20 fractions (moderate hypofractionation) as in the HHIP trial [37] or, since 2020, ultra-hypofractionated radioerapy with 42.7 Gray in 7 fractions. The ultra-hypofractioated was shown to be equally effective as the standard diotherapy in the Nordic HYPO-RT-PC trial [38]. Most vedish radiotherapy centres participated in this trial and e therefore highly experienced in planning and delivering ra-hypofractionated radiotherapy. Not least patients living away from a radiation centre appreciate avoiding the herwise long radiation treatment course. Ultra-hypofractiotion is the radiation treatment of choice for men with ermediate-risk and is considered a valid option for some, selected men with favourable localised high-risk cancer. This contrasts with the European guidelines, which still recommend ultra-hypofractionated radiotherapy in prospective clinical trials only [2].

10.2. High dose-rate brachytherapy

Combination therapy using EBRT with a high dose-rate brachytherapy boost (EBRT-BT) is available in all but one university hospital in Sweden. Randomized prospective trials [39], as well as retrospective observational studies, have reported reduced rates of progression to metastatic disease and prostate cancer mortality compared with EBRT and radical prostatectomy, particularly for high-risk and poorly differentiated cancer [40–42]. EBRT-BT is therefore the preferred radiotherapy method for men with high or very high-risk disease, provided that individual patient and cancer characteristics make the patient well suited for EBRT-BT. Examples of when a BT boost may not be the best option are gross tumour extension into the distal part of a seminal vesicle, a very large prostate (> 50 mm breadth), a large middle lobe, severe lower urinary tract symptoms, and a recent TUR-P.

HDR BT monotherapy can be considered for localised intermediate-risk prostate cancer, based on a recent systematic review with a meta-analysis [43] and national experience [44] showing high rates of disease control and low rates of severe side-effects.

10.3. Neoadjuvant, concomitant and adjuvant hormonal treatment

Patients with unfavourable intermediate-risk cancer were for many years recommended 6 months of neoadjuvant and concomitant GnRH agonist plus bicalutamide, but a recent meta-analysis showed better effect if the hormonal treatment starts at the same time as the radiotherapy [45]. The guidelines are now changed accordingly: a 6-month course of concomitant and adjuvant GnRH plus bicalutamide is recommended for patients with cancer in more than half of systematic biopsy cores, Gleason score 4+3=7 and/or 2–3 of the factors defining intermediate risk (T2b-c, Gleason score 7, PSA 10–20 ng/ml) [46]. The European guidelines recommend adding 4–6 months of hormonal treatment for all intermediate-risk patients, but studies suggest that the benefit, if any, is small for those with favourable intermediate-risk disease [46,47].

All patients with high-risk disease are recommended the same 6-month course of hormonal treatment as patients with intermediate-risk diseases. Patients with a bulky high-risk tumour or very high-risk disease are additionally recommended adjuvant hormonal treatment for 2–3 years [48,49]. The European guidelines recommend adjuvant GnRH agonist [2], but the Swedish guidelines favour bicalutamide because of its side-effect profile [50,51].

A recent report from the STAMPEDE multi-trial showed a substantially improved overall survival of adding 2 years of abiraterone to concomitant and adjuvant GnRH agonist treatment for a subgroup of men with very high-risk disease: those with at least 2 of the risk factors T3–4, Gleason score 8–10 or PSA > 40 ng/ml, or lymph-node metastasis [52]. This treatment concept is now recommended in the Swedish guidelines.

10.4. Adjuvant radiotherapy

Although randomized trials have shown no benefit from giving adjuvant radiotherapy after radical prostatectomy compared with radiotherapy at the time of biochemical relapse [53], adjuvant radiotherapy (64–70 Gy in 32–35 fractions) should be considered for the small group of patients with >10 mm cancer in the surgical margins in the absence of lymph node metastasis (pNx or pN0), particularly if there is Gleason grade 5 cancer in the margin. Radiotherapy should commence at least 3–6 months after surgery to reduce the risk of permanent urinary incontinence.

11. Primary hormonal treatment for nonmetastatic disease

In men with localised prostate cancer (cT1-2) with a moderately high PSA value (<30–50 ng/ml) and a PSA doubling time over 12 months, primary hormonal treatment does not prolong survival [48,49]. Watchful waiting is therefore the preferred management option for these patients if they are not candidates for curative treatment. In men with higher or more rapidly increasing PSA values and in men with locally advanced, non-metastatic disease, early hormonal treatment does prolong life, provided that their life expectancy is more than 5 years [48,49]. The Swedish guidelines recommend bicalutamide 150 mg once daily over GnRH agonists, based on bicalutamide's more favourable side-effect profile [50,51], which the European guidelines do not. Single-dose breast irradiation should be given before the start of bicalutamide treatment [54].

12. Conclusions

The evidence-base for diagnosing and managing men with prostate cancer is rapidly progressing. The 2022 Swedish prostate cancer guidelines include several new recommendations and some that differ from the European guidelines. Some recommendations may be controversial and we would appreciate it if those who have different opinions would share them in a letter to the Editor of the Scandinavian Journal of Urology.

Disclosure statement

In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting that none of the authors have any ongoing financial and/or business interests in any company that may be affected by the research reported in the enclosed paper.

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