College of Oncology

NATIONAL EXPERT – BASED PRACTICE GUIDELINES

PROSTATE CANCER

Guidelines V1.2021

EXPERT PANEL

These guidelines have been developed by a national multi-institutional and multidisciplinary expert working party, based on international guidelines.

COLLEGE OF ONCOLOGY

Prof. Dr. Marc Peeters – *Chairman College of Oncology*

Prof. Dr. Jacques De Grève – *Chair of the guidelines working party*

Ms. Isolde Van der Massen, MSc – *Scientific coordinator*

LEADER EXPERT PANEL

Prof. Dr. Thierry Roumeguère – *Belgian Society of Urology (SBU)*

EXPERT PANEL

Prof. Dr. Sylvie Rottey – *Belgian Society of Medical Oncology (BSMO)*

Dr. Daan De Maeseneer – *Belgian Society of Medical Oncology (BSMO)*

Prof. Dr. Raymond Oyen – *Belgian Society of Radiology (BSR)*

Prof. Dr. Olivier De Hertogh – *Belgian Society for Radiotherapy & Oncology (BeSTRO)*

Prof. Dr. Gert De Meerleer – *Belgian Society for Radiotherapy & Oncology (BeSTRO)*

Prof. Dr. Sandrine Rorive – *Belgian Society of Pathology*

Prof. Dr. Sofie Verbeke – *Belgian Society of Pathology*

Prof. Dr. Karolien Goffin – *Belgian Society of Nuclear Medicine* (*BELNUC)*

Prof. Dr. Karel Decaestecker – *Belgian Association of Urology (BVU)*

Dr. Julien Van Damme – *Belgian Society of Urology (SBU)*

Prof. Dr. Hein Van Poppel – *European Association Urology (EAU)*

INTRODUCTION

This document provides an overview of the good clinical practice guidelines for **prostate cancer** and covers a broad range of topics such as screening, diagnosis, treatment and follow-up.

These guidelines are developed by a panel of experts comprising clinicians of different specialties and designated by their respective scientific societies.

The guidelines are based on the best evidence available at the time they are derived (2021).

The aim of these guidelines is to assist all national care providers involved in the care of patients with prostate cancer and serve as a base and supporting tool for the local institutional guidelines and MOC (Multidisciplinary Oncological Consult) discussions in Belgium.

SEARCH FOR EVIDENCE

This national guideline is derived from existing international guidelines and have been updated and adapted to the Belgian context by the expert panel. The following guidelines have mostly been used: EAU guidelines 2021 (EAU-EANM-ESTRO-ESUR-ISUP-SIOG), NCCN guidelines 2021 and ESMO guidelines 2020 (Aslam N, Nadeem K, Noreen R, 2021; Mottet et al., 2021; Parker et al., 2020).

The expert panel consisted of experts in various settings and representatives of the relevant professional Belgian societies, implicated in the management of prostate cancer.

This national guideline will be regularly updated as new evidence with practice implications emerges.

The strength of each recommendation is represented by the words ‘strong’ or ‘weak’. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

LIST OF ABBREVIATIONS

ADT: androgen-deprivation therapy

AR: androgen receptor

AS: active surveillance

ASAP: atypical small acinar proliferation

BCR: biochemical recurrence

BpMRI: biparametric magnetic resonance imaging

CAP: College of American Pathologists

CMO: classification internationale des maladies pour l'oncologie

COG-TB: cognitive guided ultrasound targeted biopsies

CRPC: castration resistant prostate cancer

CT: computed tomography

DNA: deoxyribonucleic acid

DRE: digital rectal exam

EANM: European Association of Nuclear Medicine

EAU: European Association of Urology

EBRT: external beam radiotherapy

ELND: extended lymph node dissection

ERSPC: European Randomized Study of Screening for Prostate Cancer

ESMO: European Society of Medical Oncology

GS: Gleason score

GUPS: genitourinary pathology society

GY: Gray

HFX: hypofractionated

IGRT: image-guided radiation therapy

IMRT: intensity-modulated radiation therapy

IPSS: international prostate symptom score

ISUP: international society of urological pathology

LHRH: luteinizing hormone-releasing hormone

mCRPC: metastatic castration-resistant prostate cancer

mpMRI: multiparametric magnetic resonance imaging

MRI: magnetic resonance imaging

MRI-GB: magnetic resonance imaging – guided biopsy

MRI-TB: magnetic resonance imaging – targeted biopsy

MRI-TRUS: magnetic resonance imaging – transrectal ultrasound

NCCN: National Comprehensive Cancer Network

NGS: next generation sequencing

PET: positron emission tomography

PINHG: prostatic intra-epithelial neoplasia

PLN: pelvic lymph nodes

PLND: pelvic lymph node dissection

PI-RADS: prostate imaging – reporting and data system

PCPT: prostate cancer prevention trial

PSA: prostate-specific antigen

PSADT: prostate-specific antigen doubling time

PSMA: prostatic-specific membrane antigen

PSMA-PET: prostatic-specific membrane antigen – positron emission tomography

PSMA-PET/CT: prostatic-specific membrane antigen – positron emission tomography/computed tomography

RP: radical prostatectomy

SBRT: stereotactic body radiation therapy

SRP: salvage radical prostatectomy

SRT: salvage radiation therapy

TRUS: transrectal ultrasound

TRUS-GB: transrectal ultrasound –guided biopsy

TURP: Transurethral resection of the prostate

VMAT: volumetric-modulated arc therapy

WG: working group

WHO: World Health Organisation

WW: watchful waiting

DIAGNOSTIC EVALUATION

SCREENING AND EARLY DETECTION

- Early prostate-specific antigen (PSA) testing can be offered to (EAU + consensus working group (WG); strong recommendation):
    - Men > 50 years
    - Men > 45 years with a family history of prostate cancer
    - Men with African origin > 45 years
    - BRCA2 carriers > 45 years
- The healthy male population and the general practitioners need to be informed that, although getting prostate cancer cannot (probably not) be prevented, dying from prostate cancer can be prevented. The first step is always PSA testing. Following the age and the value, PSA testing should be repeated, stopped or further risk stratification needs to be done. The decision tree in the Appendix should be used (Figure 1) (Van Poppel, Hogenhout, et al., 2021; Van Poppel, Roobol, et al., 2021). (Consensus WG, strong recommendation)
- Testing for prostate cancer in men should not be done in men with a life expectancy less than 10 years. (ESMO + consensus WG, strong recommendation)
- Life expectancy can be calculated by using the following link: https://www.mdcalc.com/charlson-comorbidity-index-cci. (Consensus WG, strong recommendation)
- Risk calculators are useful to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. It is recommended to use the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator (http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators). When patients are categorized for low-risk, they will go for clinical follow-up. If patients are categorized for high-risk, they will go for multiparametric MRI (mpMRI) that will allow further risk stratification depending on the prostate imaging – reporting and data system (PI-RADS-v2) score. There has been a comparative study between the ERSPC and the prostate cancer prevention trial (PCPT) risk calculators were the ERSPC proved to be superior (Schumm, 2020). (Consensus WG, strong recommendation)

CLINICAL DIAGNOSIS

- MpMRI or biparametric MRI (bpMRI) must be performed before prostate biopsy and a standardized/structured report must be provided. (ESMO + consensus WG, strong recommendation)
- Clinicians should provide radiologists a request with relevant and obligatory information needed for performance of the optimal MRI-procedure (clinical information, serum PSA, previous biopsy, previous therapy). (Consensus WG, strong recommendation)
- Adhere to PI-RADS guidelines for mpMRI acquisition and interpretation and evaluate mpMRI results in multidisciplinary meetings with pathological feedback. (EAU, strong recommendation)

- Biopsy naive patients:
    - When mpMRI is positive (PI-RADS ≥ 3), combine targeted and systematic biopsy. (EAU, strong recommendation)
    - When mpMRI is negative (PI-RADS ≤ 2) and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision-making with the patient. (EAU, weak recommendation)
- Patients with prior negative biopsy:
    - When mpMRI is positive (PI-RADS ≥ 3), targeted biopsy is preferred if MR in-bore guidance or ultrasound fusion device is available. (EAU + consensus WG, weak recommendation)
    - When mpMRI is negative (PI-RADS ≤ 2) and clinical suspicion of prostate cancer is high, perform systematic biopsy. (EAU, strong recommendation)
- Currently, transperineal biopsies and transrectal prostate needle biopsies under antibiotic protection are equal options. There is not yet enough evidence available to recommend one over the other. The EAU recommends transperineal biopsies as the first choice for biopsies. As transperineal biopsy will most likely be the most preferred approach in the future, perform transperineal biopsies whenever possible. (Consensus WG, weak recommendation)
- Use a local anaesthetic by perineal and/or peri-prostatic infiltration for prostate needle biopsies. (EAU, weak recommendation)
- Do not offer non-targeted transition zone sampling at initial biopsies due to low detection rates. (EAU, weak recommendation)
- Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting. (EAU, strong recommendation)
- With respect to technical quality, single-core site-specific labelled submission is ideal but 2 core submission is acceptable. When more than 2 cores are submitted in a single container, there is an increased likelihood of fragmentation (Gevaert et al., 2018; Srigley et al., 2014). (Consensus WG, strong recommendation)
- Clinicians should provide to pathologists relevant clinical information needed for adequate histological diagnosis (presence of suspect area, previous biopsy, previous therapy, pre-biopsy serum PSA and clinical stage) in line with the recent International Collaboration on Cancer Reporting dataset. (Consensus WG, strong recommendation)
- The samples must be accompanied by a request for analysis with legal and obligatory communication of the information listed "*in Article 19, paragraph 1 of the Royal Decree of 5 December 2011 on the approval of pathology laboratories*". (Consensus WG, strong recommendation)
- The reporting of prostate biopsies may be done at core and specimen level. The total of cores and the number of positive cores with highest and global Gleason score (GS) need to be reported. (Consensus WG, strong recommendation)
- Each biopsy should be evaluated by using the International Society of Urological Pathology (ISUP) Consensus recommendations (van Leenders et al., 2020). (ESMO, strong recommendation)
- The Belgian working group on Uropathology wants to encourage standardised structured reporting of prostate biopsies. The followings

features should be included in the **pathology report** based on the College of American Pathologists (CAP) criteria:

- Precise location (including targeted area, if noted)
- Length of core (in mm) as measured on the glass slide
- Presence or absence of tumour
- Histological type assigned in line with the 2016 WHO: World Health Organisation (WHO) Classification (including indication if mixed types present)
- Tumour extent (millimetre's cancer length and/or percentage of cancer in each core)
- Gleason score
- Percentage of Gleason pattern 4 (and 5 if present)
- Gleason Grade Group,
- Presence of cribriform pattern
- Presence of intraductal carcinoma of the prostate
- Presence of extraprostatic extension and presence of high-grade prostatic intra-epithelial neoplasia (PINHG) and/or atypical small acinar proliferation (ASAP) in the absence of invasive carcinoma.

- Three targeted biopsies per lesion are suitable during MR in-bore or MRI ultrasound fusion biopsy, especially for lesions of PI-RADS 3 or 4, or small lesions (maximal diameter less than 1.5 cm) which may help to tailor targeted prostate biopsy procedures (Song et al., 2020). (Consensus WG, weak recommendation)
- In general, the higher the PI-RADS score (4 or 5), the lower the number of biopsies required. The lower the PI-RADS score, the more targeted biopsies are required for accuracy purposes, even if fusion techniques are used (Kenigsberg et al., 2018; Sonmez et al., 2020). (Consensus WG, weak recommendation)
- For suspicious anterior lesions, it is recommended to perform targeted deep anterior biopsies, either MR in-bore or assisted with MR-ultrasound fusion (transrectal or transperineal ultrasound – MRI fusion) techniques. 'in-bore' biopsy is rather time consuming and at the expense of diagnostic MRI-time. The ultimate choice of the biopsy technique is upon the centre's choice, depending on the local experience. Magnetic resonance imaging – guided biopsy (MRI-GB) shows similar overall prostate cancer detection rates compared with transrectal ultrasound –guided biopsy (TRUS-GB), with increased rates of clinically significant prostate cancer, and decreased rates of insignificant prostate cancer. Magnetic resonance imaging – targeted biopsy (MRI-TB) has a superior overall prostate cancer detection compared with cognitive ultrasound targeted biopsies (COG-TB). Fusion-targeted biopsy and MRI-TB appear to have similar detection rates. Head-to-head comparisons of MRI-GB techniques are still limited (Wegelin et al., 2017).
- Template biopsies (Consensus WG, strong recommendation)
  - At least 8 systematic biopsies are recommended in prostates with a size of about 30 cc. Ten to 12 core biopsies are recommended in larger prostates, with > 12 cores not being significantly more conclusive (Donovan et al., 2003; Eichler et al., 2006; Shariat & Roehrborn, 2008).

- Targeted biopsies (Consensus WG, strong recommendation)
    - Several techniques exist to perform targeted biopsy: cognitive fusion, MRI-TRUS fusion and MR in-bore biopsy. One randomized controlled trial found no significant difference in clinically significant prostate cancer detection rate for biopsy-naive patients between these 3 techniques (Wegelin et al., 2019).
    - In patients with previous negative biopsy and MRI with PI-RADS ≥ 3, MRI-TRUS fusion or MRI in-bore biopsy is recommended, if available.
    - For targeted biopsy, 2-4 biopsies per visible lesion are recommended.
    - For PI-RADS 5 lesions, 2 biopsy cores can be sufficient while for PI-RADS 3 lesions, a minimum of 4 biopsy cores are recommended for proper diagnosis (Kenigsberg et al., 2018; Sonmez et al., 2020).
- Handling of radical prostatectomy (RP) specimens is a challenging task for the pathologist. Therefore, these specimens need to be handled with great care and according to standardized protocols to enable accurate assessment of histopathological characterization (Egevad L et al., 2017; Samaratunga et al., 2011; Srigley et al., 2009). (Consensus WG, strong recommendation)
- The gold standard procedure for handling of RP specimens (according to the CAP criteria) includes:
    - Removal of seminal vesicles before weighting prostate
    - Recording of weight of prostate
    - Recording of three diameters of prostate
    - Inking of prostate with at least two colours
    - Slicing after full fixation using 10% buffer formalin saline
    - Modified cone method, apex
    - Modified cone method, base
    - Embedding of section through the base of the seminal vesicle
    - Complete embedding of prostate is the gold standard; if partial embedding is chosen, the method should be documented in the report.
- The pathological report for RP should include the following features (CAP 2021 (Gladell P. Paner et al., 2021)):
    - Type of handling procedure (see above)
    - Histologic type (acinar adenocarcinoma, ductal adenocarcinoma, small-cell neuroendocrine carcinoma, other histological type)
    - Histologic grade including GS and the ISUP/WHO Grade Group. For RP specimens, GS and Grade Group should be assigned to the dominant nodules, if present
    - Percentage of pattern 4 in GS 7 (3+4, 4+3)
    - Percentage of Gleason patterns 4 and 5 (applicable to GS greater than 7)
    - Presence of intraductal carcinoma (not identified, present, cannot be determined)
    - Presence of cribriform pattern

- Global tumour quantification
- In case of dominant tumour nodule, precise size and location
- Presence of extraprostatic extension: precise if focal or nonfocal and its location
- Presence of urinary bladder neck invasion
- Presence of seminal vesicle(s) invasion(s): precise the laterality and/or multifocality
- Presence of lymphovascular invasion
- Presence of perineural invasion (not identified, intraprostatic, intracapsular, extracapsular)
- Margin status: including the linear length of positive margin(s) in mm, the focality (unifocal/multifocal); the location(s) of positive margin(s) and the Gleason pattern at positive margin(s). In case of negative margins, specify if benign prostate gangs are present at surgical margin
- Precise if treatment effects are noticed or suggested if clinical data missing
- Regional lymph nodes status (number of lymph nodes examined, number of lymph nodes involved and presence/absence of extranodal extension)
- Pathologic stage pTNM stage classification (UICC 2017, 8th edition)
- Additional pathological findings, if present
- Ancillary studies, if performed

Histological grade and pathological stage

Table 1 International Society of Urological Pathology 2014 grade (group) system)

Grade Group	Gleason Score	Definition
1	Less than or equal to 6	Only individual discrete well-formed glands
2	3+4=7	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
3	4+3=7	Predominantly poorly formed/fused/cribriform glands with lesser component (#) of well-formed glands
4	4+4=8	Only poorly formed/fused/cribriform glands
	3+5=8	Predominantly well-formed glands and lesser component (##) lacking glands (or with necrosis)
	5+3=8	Predominantly lacking glands (or with necrosis) and lesser component (##) of well-formed glands
5	9-10	Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands (#)

TURP targets the transitional zone of the prostate. Prostate cancer isolated exclusively in the transitional zone is uncommon accounting for 2 – 7% of all prostate cancer (Perera et al., 2016). Standard handling of TURP specimens includes embedding and analysing only part of larger specimen. The CAP recommends that specimens weighting < 12 g should be examined in entirety. For specimens weighting > 12 g, the initial 12 g are submitted (6-8 cassettes) and 1 cassette may be submitted for every additional 5 g of remaining tissue (G.P. Paner et al., 2019). (Consensus WG, weak recommendation)

- In case of prostate cancer, characterisation should include (CAP recommendation, strong recommendation):
    - The histological type
    - The histological grade (GS)
    - The percentage of pattern 4 in case of GS 7
    - The percentage of patterns 4 and 5 (applicable to GS greater than 7)
    - The ISUP/WHO Grade Group, presence of cribriform pattern and/or intraductal carcinoma if present
    - An estimation of the quantitation of tumour (<10% or >10%)
    - Additional features if present.

CLASSIFICATION AND STAGING SYSTEMS

- The TNM classification (Union for International Cancer Control) can be found in the Appendix (Table 3).
- The EAU risk groups can be found in Table 2.

Table 2 EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	**Intermediate risk**	**High-risk**	
PSA < 10 ng/mL And GS < 7 (ISUP grade 1) And cT1-2a	PSA 10-20 ng/mL Or GS 7 • Favourable: ISUP 2 • Non-favourable: ISUP 3 Or cT2b	PSA > 20 ng/mL Or GS > 7 (ISUP grade 4/5) Or cT2c	Any PSA Any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

Staging and imaging

- Use pre-biopsy MRI for local staging information. (EAU, weak recommendation)

Low-risk localised disease

- Do not require additional imaging for staging purposes (EAU, strong recommendation)

Intermediate risk disease

- In ISUP grade ≥ 3, include at least cross-sectional abdominopelvic imaging and a bone scan for metastatic screening. (EAU, weak recommendation)

High-risk disease/locally advanced disease

- Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone scan. (EAU, strong recommendation)

Prostatic-specific membrane antigen – positron emission tomography (PSMA-PET) imaging

- It is strongly advised to report PSMA-PET imaging in a standardized manner, by using the E-PSMA scoring system (developed by European Association of Nuclear Medicine) (Ceci et al., 2021). (Consensus WG, strong recommendation)
- PSMA-PET is recommended for primary staging in high-risk patients, in whom the imaging may have an effect on the primary treatment that will be performed. (Consensus WG, strong recommendation)
- PSMA-PET is the imaging modality of choice in case of biochemical

recurrence (BCR). (Consensus WG, strong recommendation)

- PSMA-PET imaging can be used in the advanced setting, but criteria for response or disease progression are not well defined. (Consensus WG, weak recommendation)
- PSMA-PET is mandatory for a selection of patients for PSMA-based radioligand therapy. (Consensus WG, strong recommendation)
- Patients are referred for early salvage radiation therapy (SRT) as soon as PSA becomes detectable, if possible below a threshold value of 0.2 ng/ml. SRT should be decided on the basis of PSA, and not deferred until a PSMA-positive relapse would be detected on PET. (Consensus WG, strong recommendation)
- While reporting PSMA-PET in recurrent setting, also the clinical stage of the disease should be taken into consideration. Persistent disease after surgery (detectable PSA levels after surgery) and BCR (undetectable PSA levels after surgery), while both represent an early recurrence, are two conditions with different outcome and different incidence of detectable metastatic disease. Finally, the proper knowledge of potential pitfalls during PET image interpretation will increase its overall specificity (Ceci et al., 2021). (Consensus WG, strong recommendation)

TREATMENT

GENERAL GUIDELINES FOR THE TREATMENT OF PROSTATE CANCER

- There is no consensus regarding the optimal management of localised disease. Patients should be informed of the benefits/harms of the different options. Given the range of treatment options/side effects, men should be offered the opportunity to consult with both an urologist and a radiation oncologist. (ESMO, strong recommendation)
- Patients should also be informed of the benefits/harms of not getting treatment. An untreated prostate cancer may also cause sexual dysfunction, infertility, bowel and urinary problems. (Consensus WG, strong recommendation)
- Offer watchful waiting (WW) policy to asymptomatic patients with life expectancy < 10 years based on co-morbidities. (EAU, strong recommendation)
- **Surgical treatment**
    - Inform patients that no surgical approach (open, laparoscopic- or robotic RP) has clearly shown superiority in terms of functional or oncological results. (EAU, weak recommendation)
    - Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, nomogram, mpMRI). (EAU, weak recommendation)
    - When a lymph node dissection is deemed necessary, perform an extended lymph node dissection (eLND) template for optimal staging. (EAU, strong recommendation)
    - Do not offer neoadjuvant androgen-deprivation therapy (ADT) before surgery. (EAU, strong recommendation)
- **Radiotherapeutic treatment**
    - Offer intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) for definitive treatment of prostate cancer by external beam radiotherapy (EBRT). (EAU, strong recommendation)
    - Offer moderate hypofractionated (HFX) with IMRT/VMAT, including image-guided radiation therapy (IGRT) to the prostate, to carefully selected patients with localized disease. Ensure that moderate HFX adheres to radiotherapy protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in 4 weeks or 70 Gy/28 fractions in 6 weeks. (EAU, strong recommendation)
- **Active therapeutic options outside surgery and radiotherapy**
    - Offer high-intensity focused US within a clinical trial setting or well-designed prospective cohort study. (EAU, strong recommendation)
    - Only offer focal therapy within a clinical trial setting or well-designed prospective cohort study. (EAU, strong recommendation)

IGRT TREATMENT (Ghadjar et al., 2019)

- IGRT for prostate cancer needs to be based on the position of the prostate itself, IGRT based on bony anatomy is considered inadequate for prostate only treatments. (ESTRO consensus guideline)
- IGRT to account for interfractional prostate movement for conventionally fractionated and moderately HFX EBRT as a minimum standard must be based on either fiducial markers or CT-based approaches with soft-tissue matching. A combination of fiducial markers with CT-based approaches is preferred. (ESTRO consensus guideline)
- Visualisation of implanted fiducial markers or CT-based image guidance are options for prostate IGRT. (Consensus WG, strong recommendation)
- Daily on-line correction is recommended for any kind of fractionated radiotherapy. (Consensus WG, strong recommendation)
- For a treatment of both the prostate and pelvic lymph nodes (PLN), IGRT is preferentially based the position of the prostate. IGRT based on the bony structures may be considered but margins for prostate should then be enlarged compared to the sizes suggested in Table 4, in order to accommodate prostate organ motion. (ESTRO consensus guideline)
- A distended rectum in the planning CT should be prevented as it may deform the prostate. (ESTRO consensus guideline)
- Bowel regimens (including diets) are not recommended as routine practice. However, for patients with a high degree of intrafractional motion, they may be indicated. Dietetic counselling should be offered as part of a multidisciplinary approach to pelvic radiotherapy. (Consensus WG, strong recommendation)
- Bladder filling protocols have no clear effect on positioning stability of the prostate, but may ensure a dosimetric advantage in terms of bladder and bowel sparing as they move the bowel and parts of the bladder out of the high-dose volume. (ESTRO consensus guideline)
- Monitoring and ideally tracking of intrafraction motion of the prostate may be considered for extreme hypofractionation. The use of PEG-based spacers could be discussed in that setting to further decrease the dose to the anterior rectal wall. (Consensus WG, strong recommendation)
- Margins for the three most popular IGRT scenarios have been suggested as examples in Table 4 (Appendix). Centers should however make an effort to estimate the residual error in their own institution and derive safe margins from these estimates. (ESTRO consensus guideline)

TREATMENT BY DISEASE STAGES

Treatment of low-risk disease

1. Active surveillance

- Offer AS to patients with a life expectancy > 10y and low-risk disease. (EAU, strong recommendation)
- If a patient has had mpMRI followed by systematic and targeted biopsies there is no need for confirmatory biopsies. (EAU, weak recommendation)
- Patients with intraductal and cribriform histology on biopsy should be excluded from AS. (EAU, strong recommendation)
- Perform a mpMRI before a confirmatory biopsy if no mpMRI has been performed before the initial biopsy. (EAU, strong recommendation).

- Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed. (EAU, strong recommendation)
- Perform serum PSA assessment every 6 months. (EAU, strong recommendation)
- Perform DRE every 12 months. (EAU, strong recommendation)
- Confirmatory biopsy needs to be done after 1 year and repeat prostate biopsy after every 3 to 5 years. Repeat biopsy should be omitted in case of negative MRI and low suspicion of PCa progression.
- It is unclear whether protocol-mandated MRI should be performed in the absence of any triggers. (EAU, weak recommendation)
- If the PSA doubling time (PSADT) is less than 1 year, then repeat biopsy is recommended. (Consensus WG, strong recommendation).
- During follow-up, if mpMRI is negative (i.e., PI-RADS < 3), and clinical suspicion of prostate cancer progression is low (e.g. low PSA velocity, long PSADT), omit biopsy based on shared decision making with the patient. (EAU, weak recommendation)
- Counsel patients about the possibility of needing further treatment in the future. (EAU, strong recommendation)

2. Active treatment

- Offer surgery and radiotherapy as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression. (EAU, weak recommendation)

2.1 Prostatectomy

2.2 PLND

- Do not perform PLND. (EAU, strong recommendation) (estimated risk for pN+<5%). The Briganti nomogram can be used: https://www.evidencio.com/models/show/917.

2.3 Radiotherapeutic treatment

- Offer low-dose rate brachytherapy to patients with low-risk prostate cancer, without a recent TURP, with an IPSS ≤ 12 (ideally up to 8) and a prostate volume < 50 mL (ideally less than 40). (EAU + consensus WG, strong recommendation)
- Use IMRT with a total dose of 74-80 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), without ADT. (EAU, strong recommendation)

2.4 Other therapeutic options

- Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment. (EAU, strong recommendation)
- Only offer whole gland treatment (such as high-intensity focused ultrasound, etc.) or focal treatment within a clinical trial setting or well-designed prospective cohort study. (EAU, strong recommendation)

Treatment intermediate risk (EAU)

1. Active surveillance (AS)

- Offer AS to highly selected patients (< 10% pattern 4) accepting the 3-fold higher increased risk of further metastases as compared to patients harbouring ISUP 1 prostate cancer. (EAU, weak recommendation)

- Patients with intraductal and cribriform histology on biopsy should be excluded from AS. (EAU, strong recommendation)

2. RP

- Offer RP to patients with intermediate-risk disease and a life expectancy of > 10 years. (EAU, strong recommendation)
- Offer nerve-sparing surgery to patients with a low risk of extracapsular disease. (EAU, strong recommendation)

3. ePLND

- Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%. (EAU, strong recommendation)

4. Radiotherapeutic treatment

- Offer low-dose rate brachytherapy to selected patients: patients without a recent TURP, with an IPSS ≤ 12 and a prostate volume < 50 mL. (EAU, strong recommendation)
- For EBRT, use a total dose of 76-78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term neoadjuvant plus concomitant ADT (4 to 6 months). (EAU, strong recommendation)
- Stereotactic body radiation therapy (SBRT) is an emerging alternative for intermediate risk prostate cancer. At the moment, a national prostate SBRT group is being set up to define best practices and prospectively follow patients' outcome. (Consensus WG, weak recommendation)
- Prostate SBRT to a minimal dose of 36.25 Gy in 5 fractions of 7.25 Gy may be offered to selected patients as an alternative, preferably in the setting of a prospective trial. (Consensus WG, weak recommendation)
- In patients not willing to undergo ADT, use an escalated dose of EBRT (at least 76 Gy) or a combination with brachytherapy (Chollet et al., 2011). (Consensus WG, weak recommendation)

5. Other therapeutic options

- Whole-gland ablative therapy or focal ablative therapy for intermediate-risk disease should only be offered within a clinical trial setting or well-designed prospective cohort study. (EAU, strong recommendation)
- Do not offer ADT monotherapy to intermediate-risk asymptomatic men. (EAU + consensus WG, weak recommendation)

Treatment high risk

There are two equal options for treatment of high risk patients: surgery and radiotherapy.

1. RP and ePLND

- Offer RP to selected patients with high-risk localised prostate cancer, as part of potential multi-modal therapy combined with ePLND. (EAU + consensus WG, strong recommendation)
- Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure. (EAU, strong recommendation)

2. Radiotherapeutic treatment

- Use EBRT with at least 76 Gy in combination with long-term ADT (18-24 months). (Consensus WG, strong recommendation)

- Use EBRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (18-24 months) (Boer & Schröder, 1999). (Consensus WG, strong recommendation)
- The panel does not recommended the addition of docetaxel to ADT plus EBRT in patients with high and very-high risk prostate cancer. The panel does not recommended the addition of docetaxel to ADT plus EBRT in patients with high and very-high risk prostate cancer. (NCCN, strong recommendation)
- There is randomized evidence and a review supporting the role of pelvic radiotherapy over prostate only radiotherapy in very high-risk patients. (Consensus WG, strong recommendation)

3. Therapeutic options outside surgery and radiotherapy

- Do not offer whole gland or focal therapy to high-risk patients. (EAU, strong recommendation)
- Do not use ADT monotherapy in asymptomatic patients. (EAU, strong recommendation)
- Do not offer neoadjuvant ADT regimen before prostatectomy in high/very high risk patients (outside a clinical trial). (Consensus WG, strong recommendation)
- Docetaxel should not be offered before (neoadjuvant) local therapy for high risk localized prostate cancer (Eastham et al., 2020; Fizazi et al., 2018). (Consensus WG, strong recommendation)

Treatment locally advanced prostate cancer

- Offer patients with cN1 disease a local treatment (either RP or IMRT plus IGRT) plus long-term ADT. (EAU, weak recommendation)

1. RP

- Offer RP to selected patients with locally-advanced prostate cancer as part of multi-modal therapy. (EAU, strong recommendation)

2. EPLND

- Perform an ePLND prior to RP in locally-advanced prostate cancer. (EAU, strong recommendation)

3. Radiotherapeutic treatments

- In patients with locally-advanced disease, offer IMRT plus IGRT in combination with long-term ADT. (EAU, strong recommendation)
- Offer long-term ADT for at least 18-24 months. (EAU, weak recommendation)

4. Therapeutic options outside surgery and radiotherapy

- Do not offer whole gland treatment or focal treatment to high-risk patients. (EAU, strong recommendation)
- Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a PSADT < 12 months, and either a PSA > 50 ng/mL, a poorly-differentiated tumour or troublesome local disease-related symptoms. (EAU, strong recommendation)
- Offer patients with cN1 disease a local treatment (either RP or EBRT) plus long-term ADT. (EAU, strong recommendation)

Adjuvant treatment after RP

1. **Guidelines for ADT in pN0 patients**

- Do not prescribe adjuvant ADT in pN0 patients. (EAU, strong recommendation)
- Only offer adjuvant IMRT plus IGRT to high-risk patients (pN0) with at least two out of three high-risk features (ISUP grade group 4–5, pT3 ± positive margins). (EAU, strong recommendation)
- Discuss three management options with patients with pN1 disease after an ePLND, based on nodal involvement characteristics (EAU, weak recommendation):
    1. Offer adjuvant ADT;
    2. Offer adjuvant ADT with additional IMRT plus IGRT;
    3. Offer observation (expectant management) to a patient after eLND and < 2 nodes and a PSA < 0.1 ng/mL.

2. **Guidelines for non-curative or palliative treatments in prostate cancer**

- WW for localized prostate cancer
    - Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy. (EAU, strong recommendation)
- WW for locally-advanced prostate cancer
    - Offer a deferred treatment policy using ADT monotherapy to M0 asymptomatic patients with a PSADT > 12 months, a PSA < 50 ng/mL and well-differentiated tumour, who are unwilling or unable to receive any form of local treatment. (EAU, weak recommendation)

Persistent PSA after RP

- Offer a PSMA-PET scan to men with a persistent PSA > 0.2 ng/mL if the results will influence subsequent treatment decisions. (EAU, weak recommendation)
- Treat men with no evidence of metastatic disease with SRT and additional hormonal therapy. (EAU, weak recommendation)

Management of PSA-only recurrence after treatment with curative intent

1. **Imaging in patients with BCR**

PSA recurrence after RP

- Perform PSMA-PET/CT if the results will influence subsequent treatment decisions. (EAU, weak recommendation)
- In case PSMA-PET/CT is not available, and the PSA level is > 1 ng/mL, perform fluciclovine PET/CT or choline PET/CT imaging if the results will influence subsequent treatment decisions. (EAU, weak recommendation)

PSA recurrence after radiotherapy

- Perform prostate mpMRI to localize abnormal areas and guide biopsies in patients fit for local SRT. (EAU, weak recommendation)
- Perform PSMA-PET/CT (if available) or fluciclovine PET/CT or choline PET/CT in patients fit for curative salvage treatment. (EAU, strong recommendation)

- Dynamic contrast-enhanced MR imaging in this setting is of much greater importance than for the clinical application covered by PI-RADS, and in most recurrence settings dynamic contrast-enhanced imaging is the most sensitive and accurate sequence. (NCCN, strong recommendation)
- Addition of diffusion-weighted imaging with background body signal suppression to whole-body MRI allows assessment for bone and soft-tissue metastasis. Recently, a scoring system—Metastasis Reporting and Data System for Prostate Cancer (MET-RADSP)—using whole-body MRI was proposed for comprehensive assessment of prostate cancer metastasis (Padhani et al., 2017). (Consensus WG, weak recommendation)

2. Guidelines for second-line therapy with curative intent

2.1 Recommendations for BCR after RP

- Offer monitoring, including PSA, to EAU low-risk BCR patients. (EAU, weak recommendation)
- Offer early salvage IMRT plus IGRT to men with two consecutive PSA rises. (EAU, strong recommendation)
- A negative PET/CT scan should not delay SRT, if otherwise indicated. (EAU, strong recommendation)
- Do not wait for a PSA threshold before starting treatment. Once the decision for SRT has been made, SRT (at least 66 Gy) should be given as soon as possible. (EAU, strong recommendation)
- Offer hormonal therapy in addition to SRT to men with BCR. (EAU, weak recommendation)

2.2 Recommendations for BCR after radiotherapy

- Offer monitoring, including PSA to EAU low-risk BCR patients. (EAU, weak recommendation)
- Only offer SRP, brachytherapy, high-intensity focused ultrasound, cryosurgical ablation or surgery to highly selected patients with biopsy proven local recurrence within a clinical trial setting or well-designed prospective cohort study undertaken in experienced centres. (EAU + consensus WG, strong recommendation)
- SRP should only be performed in experienced centres. (EAU, weak recommendation)

2.3 Recommendation for systemic salvage treatment

- Do not offer ADT to M0 patients with a PSADT > 12 months. (EAU, strong recommendation)

Treatment metastatic prostate cancer

- Offer immediate systemic treatment with ADT to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, and ureteral obstruction) to M1 symptomatic patients. (EAU, strong recommendation)
- Offer LHRH agonists or antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction. (EAU + consensus WG, weak recommendation)
- Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord

compression or pathological fracture. (EAU, strong recommendation)

- Offer immediate systemic treatment also to M1 patients asymptomatic from their tumour. (EAU, weak recommendation)
- Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side-effects, provided the patient is closely monitored. (EAU, weak recommendation)
- Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon. (EAU, weak recommendation)
- Do not offer AR antagonists monotherapy to patients with M1 disease. (EAU, strong recommendation)
- Discuss combination therapy including ADT plus systemic therapy with all M1 patients. (EAU, strong recommendation
- Do not offer ADT monotherapy to patients whose first presentation is M1 disease is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy and are willing to accept the increased risk of side effects (EAU, strong recommendation)
- Combine ADT with chemotherapy/abiraterone acetate+prednisone/apalutamide/enzalutamide to patients who are fit enough for these treatments. (Consensus WG, strong recommendation)
- Offer ADT combined with prostate radiotherapy (using the doses from the STAMPEDE study or an equivalent biological dose) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria. (EAU, strong recommendation)
- Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control). (EAU, strong recommendation)
- Do not offer ADT combined with surgery to M1 patients outside of clinical trials. (EAU, strong recommendation)
- If clinical studies concerning metastasis-directed therapy are running, it is advised to put patients into such a study. However, if such studies are absent, well-informed patients can be treated with metastasis-directed therapy. (Consensus WG, strong recommendation).

Treatment castration-resistant prostate cancer (CRPC)

Life-prolonging treatments of castrate-resistant disease

- Ensure that testosterone levels are confirmed to be < 50 ng/dL before diagnosing CRPC. (EAU, strong recommendation)
- Counsel, manage and treat patients with mCRPC in a multidisciplinary team. (EAU, strong recommendation)
- Treat patients with mCRPC with life-prolonging agents. (EAU, strong recommendation)
- Offer mCRPC patients somatic and/or germline molecular testing as well as testing for mismatch repair deficiencies or microsatellite instability. (EAU, strong recommendation)

Systematic treatments of castrate-resistant disease

- Base the choice of treatment on the performance status, symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on the previous treatment for hormone-sensitive metastatic prostate cancer (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, radium-223). (EAU + consensus WG, strong recommendation)
- Offer patients with mCRPC who are candidates for cytotoxic therapy and are chemotherapy naïve docetaxel with 75 mg/m^2 every 3 weeks. (EAU, strong recommendation)
- Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA homologous recombination repair alterations. (EAU, strong recommendation)
- Base further treatment decisions of mCRPC on performance status, previous treatments, symptoms, co-morbidities, genomic profile, extent of disease and patient preference. (EAU, strong recommendation)
- Offer abiraterone or enzalutamide to patients previously treated with one or two lines of chemotherapy. (EAU, strong recommendation)
- Avoid sequencing of AR targeted agents. (EAU, weak recommendation)
- Offer chemotherapy to patients previously treated with abiraterone or enzalutamide. (EAU, strong recommendation)
- Offer cabazitaxel to patients previously treated with docetaxel. (EAU, strong recommendation)
- Offer cabazitaxel to patients previously treated with docetaxel and progressing within 12 months of treatment with abiraterone or enzalutamide. (EAU, strong recommendation)
- Offer poly(ADP-ribose) polymerase inhibitors to pre-treated mCRPC patients with relevant DNA repair gene mutations. (EAU, strong recommendation)

Guidelines for supportive care of castrate-resistant disease

- Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications. (EAU, strong recommendation)
- Monitor serum calcium and offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates. (EAU, strong recommendation)
- Treat painful bone metastases early on with palliative measures such as EBRT, and adequate use of analgesics. (EAU, strong recommendation)
- In patients with spinal cord compression start immediate high-dose corticosteroids and assess for spinal surgery followed by irradiation. Offer radiation therapy alone if surgery is not appropriate. (EAU, strong recommendation)

Guideline for non-metastatic castrate-resistant disease

- Offer (when available) apalutamide, darolutamide or enzalutamide to patients with M0 CRPC and a high risk of developing metastasis (PSADT < 10 months) to prolong time to metastases and overall survival. (EAU, strong recommendation)

FOLLOW-UP

Follow-up after local treatment: follow-up treatment with curative intent

- Routinely follow up asymptomatic patients by obtaining at least a disease-specific history and serum PSA measurement. These should be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and then annually. (EAU, strong recommendation)
- At recurrence, only perform imaging if the result will affect treatment planning. (EAU, strong recommendation)

Follow-up during first line hormonal treatment (androgen sensitive period)

- The follow-up strategy must be individualized based on stage of disease, prior symptoms, prognostic factors and the treatment given. (EAU, strong recommendation)
- In patients with stage M0 disease, schedule follow-up at least every 6 months. As a minimum requirement, include a disease-specific history, serum PSA determination, as well as liver and renal function in the diagnostic work-up. (EAU, strong recommendation)
- In patients with stage M1 disease, schedule follow-up every 3 to 6 months. (EAU, strong recommendation)
- In patients on long-term ADT, measure initial bone mineral density to assess fracture risk. (EAU, strong recommendation)
- During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT. (EAU, strong recommendation)
- As a minimum requirement, include a disease-specific history, hemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and hemoglobin A1C level measurements. (EAU, strong recommendation)
- Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression. (EAU, strong recommendation)
- When disease progression is suspected, restaging is needed and the subsequent follow-up adapted/individualized. (EAU, strong recommendation)
- In M1 patients perform regular imaging (CT and bone scan) even without PSA progression. (EAU, weak recommendation)
- In patients with suspected progression, assess the testosterone level. By definition, CRPC requires a testosterone level < 50 ng/dL (< 1.7 nM/L). (EAU, strong recommendation)

PERSONALIZED MEDICINE

The Personalized Medicine commission (ComPerMed) is a committee that has developed Next Generation Sequencing (NGS) workflows. DNA sequencing using the NGS technique makes it possible to personalize treatment and optimize the management of patients with cancer. The workflow for prostate cancer can be found here: https://www.compermed.be/en/workflows/prostate.

Appendix

Table 3 Clinical Tumour Node Metastasis (TNM) classification of prostate cancer

T – Primary Tumour (stage based on digital rectal examination (DRE) only)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is not palpable	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate	
T3	Tumour extends through the prostatic capsule	
	T3a	Extraprostatic extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall.	
N – Regional (pelvic) Lymph nodes[1]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M – distant metastasis[2]		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] Metastasis no larger than 0.2 cm can be designated pNmi

[2] When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

Table 4 examples for target margins for prostate, seminal vesicles and pelvic node according to IGRT approaches (off-line, on-line with prostate tracking)

Correction protocol	Margins (mm)		
	Prostate	Seminal Vesicles*	Pelvic Nodes*
Off-line**	*LR:* 5–7 *AP:* 7–9 *CC:* 7–9	*LR:* 7–9 *AP:* 8–12 *CC:* 8–12	*LR:* 7–9 *AP:* 7–9 *CC:* 7–9
On-line	Iso: 4–6	*LR:* 5–6 *AP:* 7–9 *CC:* 7–9	*LR:* 7–8 *AP:* 7–8 *CC:* 7–8
On-line + tracking	Iso: 2–4	N/A	N/A

Iso = isotropic; N/A: not applicable; LR: left–right; AP: anterior-posterior; CC: cranial-caudal; *based on prostate matching; **without further corrections after the first correction of systematic error

(Van Poppel, Roobol, et al., 2021)

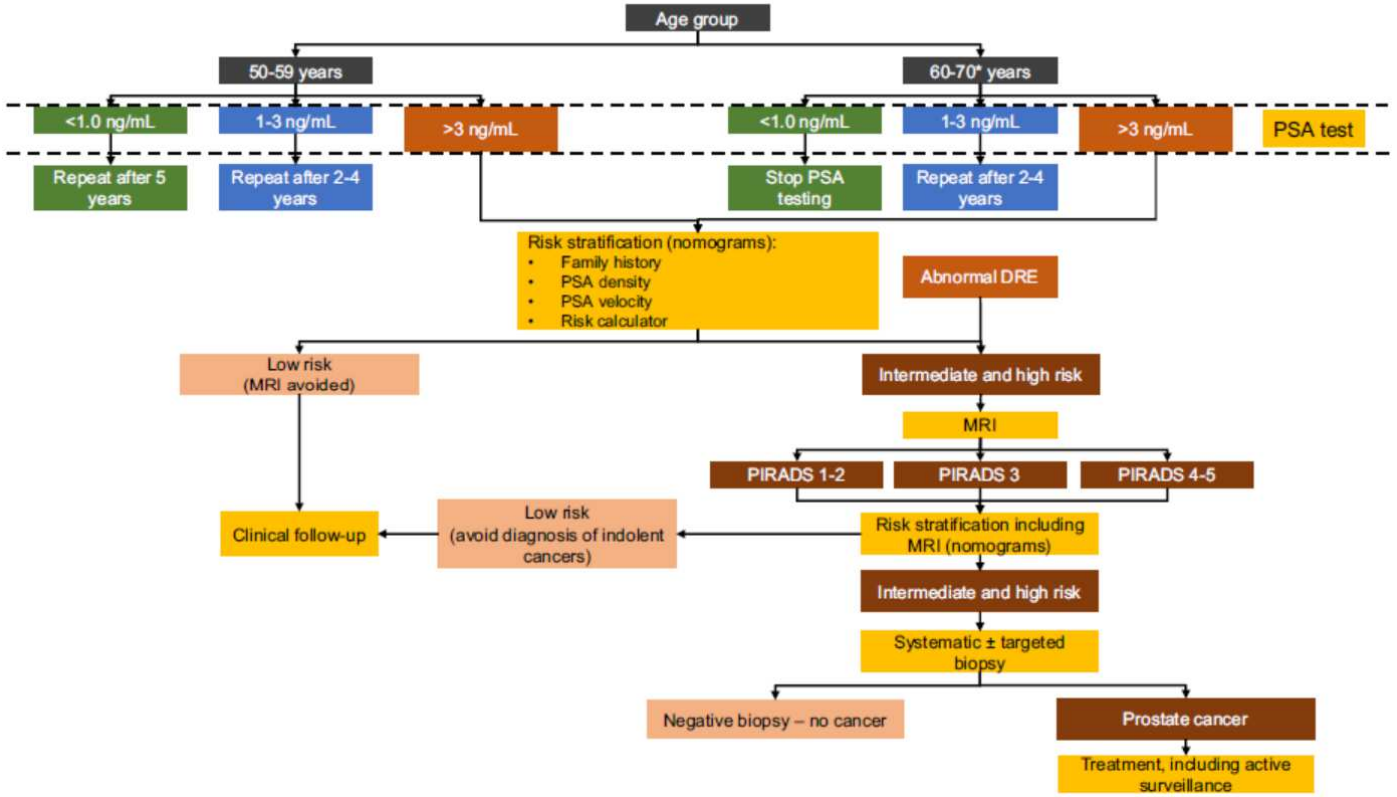

Figure 1 Risk-adapted algorithm for the early detection of prostate cancer, adapted based on prostate cancer guidelines published by the EAU. The patient's values and preferences should always be taken into account as part of a shared decision-making process. DRE = digital rectal examination; EAU = European Association of Urology; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

* Healthy men > 70 yr without important comorbidities and a life expectancy of > 10-15 yr may continue PSA testing

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