EAU-ESTRO-ESUR-SIOG GUIDELINES ON PROSTATE CANCER

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Introduction

Prostate cancer (PCa) is a complex disease, in which disease characteristics, age, comorbidities and individual patient preference will impact treatment choice. All available management options need to be discussed, in full, with the patient.

Epidemiology and Risk Prevention

Prostate cancer is the second most common cancer in males. It is a major health concern, especially in developed countries due to the greater proportion of elderly men in the general population, and the potential risk of over-treatment following early diagnosis. There are three well-established risk factors for PCa: increasing age, ethnic origin, and genetic predisposition. There is currently no high-level evidence that preventative measures may reduce the risk of PCa.

Classification and Staging Systems

The 2017 Tumour Node Metastasis (TNM) classification is used for staging (Table 1).

Table 1: 2017 TNM classification

T - Primary Tumour		
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	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule*	
	T3a	Extracapsular 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 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)

** Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.*

[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.

Pathological staging (pTNM) is based on histopathological tissue assessment and largely parallels the clinical TNM, except for clinical stage T1c and the T2 substages. All histopathologically confirmed organ-confined PCas after radical prostatectomy (RP) are pathological stage T2 and the current UICC no longer recognises pT2 substages.

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 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

Recommendations for screening and early detection	Strength rating
Do not subject men to prostate-specific antigen (PSA) testing without counselling them on the potential risks and benefits.	Strong
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status (PS) and a life-expectancy of at least ten to fifteen years.	Strong
Offer early PSA testing in well-informed men at elevated risk of having PCa: • men > 50 years of age; • men > 45 years of age and a family history of PCa; • African-Americans > 45 years of age.	Strong
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of two years for those initially at risk: • men with a PSA level of > 1 ng/mL at 40 years of age; • men with a PSA level of > 2 ng/mL at 60 years of age. Postpone follow-up to eight years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and PS; men who have a life-expectancy of < 15 years are unlikely to benefit.	Strong

Diagnostic Evaluation

Clinical diagnosis

Prostate cancer is usually suspected on the basis of digital rectal examination (DRE) and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma in prostate biopsy cores or unexpected discovery in specimens from transurethral resection of the prostate (TURP) or prostatectomy for benign prostatic enlargement.

The decision whether to proceed with further diagnostic or staging work-up is guided by which treatment options are available to the patient, taking the patient's life expectancy into consideration. Diagnostic procedures that will not affect the treatment decision can usually be avoided.

A biopsy pathology report includes the type of carcinoma and parameters describing its extent (e.g. proportion of positive cores, percentage or mm of carcinoma involvement per core) as well as Gleason score (GS) per biopsy site and global GS. Reporting of a radical prostatectomy (RP) specimen includes type of carcinoma, global GS, pathological stage and surgical margin status.

The International Society of Urological Pathology (ISUP) World Health Organization (WHO) 2014 grade groups were adopted which allow patients to better understand the behaviour of their diagnosed prostate carcinoma, while separating GS 7 adenocarcinoma into two prognostically very distinct categories; grade group 2 for GS 7(3+4) and grade group 3 for GS 7(4+3) (see Table 3).

Table 3: ISUP 2014 grade groups

Gleason score	Grade group
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

Recommendations for clinical diagnosis of PCa	Strength rating
Do not use transurethral resection of the prostate as a tool for cancer detection.	Strong
Use the International Society of Urological Pathology (ISUP) 2014 Gleason grading system for grading of PCa.	Strong
In symptomatic men, base the initial decision to perform a biopsy on prostate-specific antigen testing and digital rectal examination.	Strong
Do not initially offer transition zone biopsies due to low detection rates.	Weak
For initial diagnosis, perform a core biopsy of ten to twelve systematic transrectal or transperineal peripheral zone biopsies under ultrasound guidance.	Strong
Perform transrectal prostate needle biopsies under antibiotic protection.	Strong
Use a local anaesthetic by periprostatic infiltration for transrectal prostate needle biopsies.	Strong

Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	Strong
Adhere to the 2010 ISUP Consensus Meeting Guidelines for processing and reporting of prostatectomy specimens.	Strong

Recommendations for processing prostatectomy specimens	**Strength rating**
Ensure total embedding, by conventional (quadrant) or whole-mount sectioning.	Strong
Ink the entire surface before cutting, to evaluate the surgical margin.	Strong
Examine the apex and base separately, using the cone method with sagittal or radial sectioning.	Strong

Recommendations for repeat-biopsy imaging	**Strength rating**
Before repeat biopsy, perform multiparametric magnetic resonance imaging (mpMRI) when clinical suspicion of PCa persists in spite of negative biopsies.	Strong
During repeat biopsy include systematic biopsies and targeting of any mpMRI lesions seen.	Strong

Guidelines for staging

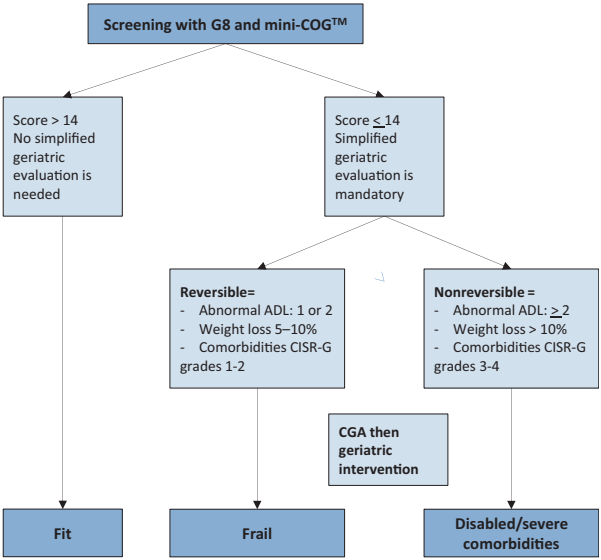
Any risk group staging	**Strength rating**
Do not use computed tomography and transrectal ultrasound for local staging.	Strong

Low-risk localised PCa	Strength rating
Do not use additional imaging for staging purposes.	Strong

Intermediate-risk PCa	Strength rating
In predominantly Gleason pattern 4 (≥ ISUP 3) use prostate multiparametric magnetic resonance imaging (mpMRI) for local staging.	Weak
In predominantly Gleason pattern 4, include at least a cross-sectional abdominopelvic imaging and bone-scan for metastatic screening.	Weak

High-risk localised PCa/locally advanced PCa	Strength rating
Use prostate mpMRI for local staging.	Strong
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong

Figure 1: Decision-making based on health status assessment (men > 70 years)*



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Mini-COG™ = cognitive test; ADL = activities of daily living; CIRS-G = cumulative illness rating score-geriatrics; CGA = comprehensive geriatric assessment.

Recommendations for evaluating health status and life expectancy	Strength rating
Systematically screen the health status of older (> 70 years) men with PCa (Figure 1).	Strong
Use the Geriatric-8 and mini-COG tools for health status screening.	Weak
Perform a full specialist geriatric evaluation in patients with G8 score ≤ 14.	Strong
Consider standard treatment in frail patients with reversible impairments (after resolution of geriatric problems) similar to fit patients, if life expectancy is > 10 years.	Weak
Offer adapted treatment in patients with irreversible impairment.	
Offer palliation in patients with poor health status.	

Disease Management

Deferred treatment

Many men with localised PCa will not benefit from definitive treatment, and 45% of men with PSA-detected PCa may be candidates for deferred management.

In men with comorbidity and a limited life expectancy, treatment of localised PCa may be deferred to avoid loss of quality of life (QoL).

Primary treatment of PCa

General recommendations for active treatment	Strength rating
Inform patients that no active treatment modality has shown superiority over any other management options in terms of survival.	Strong

Inform patients that all active treatments have side effects.	Strong
Surgical treatment	
Inform patients that no surgical approach (open, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.	Strong
Perform an extended pelvic LND (ePLND), when a LND is deemed necessary.	Strong
Do not perform nerve-sparing surgery when there is a risk of extracapsular extension (based on cT stage, GS, nomogram, multiparametric magnetic resonance imaging).	Strong
Do not offer neoadjuvant androgen deprivation therapy before surgery.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiation therapy (IMRT) or volumetric arc external-beam radiotherapy (VMAT) for definitive treatment of PCa by external-beam radiation therapy (EBRT).	Strong
Only offer moderate hypofractionation (HFX) with IMRT/VMAT, including image-guided radiation therapy (IGRT) to the prostate, to carefully selected patients with localised disease.	Strong
Ensure that moderate HFX adheres to radiotherapy (RT) protocols from trials with equivalent outcome and toxicity, i.e. 60 Gy/20 fractions in four weeks or 70 Gy/28 fractions in six weeks.	Strong

Active therapeutic options outside surgery and radiotherapy	
Only offer cryotherapy and high-intensity focused ultrasound within a clinical trial setting.	Strong
Only offer focal therapy within a clinical trial setting.	Strong

Guidelines for first line treatment of various disease stages		Strength rating
Low-risk disease		
Watchful waiting (WW)	Offer a WW policy to asymptomatic patients with a life expectancy < 10 years (based on comorbidities).	Strong
Active surveillance (AS)	Offer AS to patients suitable for curative treatment but with low-risk PCa.	Strong
	Perform multiparametric magnetic resonance imaging (mpMRI) before a confirmatory biopsy.	Strong
	During confirmatory biopsy include systematic and targeted biopsies.	Strong
	Base follow up on digital rectal examination, prostate-specific antigen (PSA) and repeat biopsies.	Strong
	Counsel patients about the possibility of needing further treatment in the future.	Strong

Active treatment	Offer surgery and radiotherapy (RT) as alternatives to AS to patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression.	Weak
Pelvic lymph node dissection (PLND)	Do not perform a PLND (estimated risk for pN+ < 5%).	Strong
Radiotherapy	Offer low-dose rate (LDR) brachytherapy to patients with low-risk PCa, without a previous transurethral resection of the prostate (TURP) and with a good International Prostatic Symptom Score (IPSS) and a prostate volume < 50 mL.	Strong
	Use intensity-modulated radiation therapy (IMRT) with a total dose of 74-80 Gy, without androgen deprivation therapy (ADT).	Strong
	Offer moderate hypofractionation (HFX) (68 Gy/20 fx in four weeks or 70 Gy/28 fractions (fx) in six weeks) as an alternative treatment option.	Strong
Other options	Only offer whole gland treatment (such as cryotherapy, HIFU, etc.) or focal treatment within a clinical trial setting.	Strong

Intermediate-risk disease		
Active surveillance	Offer AS to highly selected patients (< 10% pattern 4) accepting the potential increased risk of further metastases.	Weak
Radical prostatectomy (RP)	Offer RP to patients with intermediate-risk disease and a life expectancy > 10 years.	Strong
	Offer nerve-sparing surgery to patients with a low risk of extracapsular disease (refer to nomograms).	strong
Extended pelvic lymph node dissection (ePLND)	Perform an ePLND in intermediate-risk disease if the estimated risk for positive lymph nodes exceeds 5%.	Strong
Radiotherapy	Offer LDR brachytherapy to selected patients; patients without a previous TURP and with a good IPSS and a prostate volume < 50 mL.	Strong
	For EBRT, use a total dose of 76-78 Gy, in combination with short-term neoadjuvant plus concomitant ADT (four to six months).	Strong
	In patients not willing to undergo ADT, use an escalated dose of EBRT (76-80 Gy) or a combination with brachytherapy.	Weak

Other options	Only offer whole gland treatment (such as cryotherapy, HIFU, etc.) or focal treatment within a clinical trial setting.	Strong
High-risk localised disease		
Radical prostatectomy	Offer RP to patients with high-risk localised PCa and a life expectancy of > 10 years only as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk disease.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapy	In patients with high-risk localised disease, use ERBT with 76-78 Gy in combination with long-term ADT (two to three years).	Strong
	In patients with high-risk localised disease, use EBRT with brachytherapy boost (either HDR or LDR), in combination with long-term ADT (two to three years).	Weak
Other options	Do not offer either whole gland or focal treatment to high-risk patients.	Strong
	Do not use ADT monotherapy in asymptomatic patients.	Strong

Locally-advanced disease		
Radical prostatectomy	Offer RP to highly selected patients with (cT3b-T4 N0 or any T N1) only as part of multi-modal therapy.	Strong
Extended pelvic lymph node dissection	Perform an ePLND in high-risk PCa.	Strong
	Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapy	In patients with locally advanced cN0 disease, offer RT in combination with long-term ADT.	Strong
	Offer long-term ADT for two to three years.	Weak
Other options	Do not offer whole gland treatment or focal treatment to high-risk patients.	Strong
	Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment and who are either symptomatic or asymptomatic, but with a PSA-doubling time (DT) over twelve months or a PSA > 50 ng/mL or a poorly differentiated tumour.	Strong

Adjuvant treatment after radical prostatectomy		
	Only discuss adjuvant treatment in men with a post-operative PSA < 0.1 ng/mL.	Strong
	Do not prescribe adjuvant ADT in pN0 patients.	Strong
	Offer adjuvant EBRT to the surgical field to patients at increased risk of local relapse: pT3 pN0 with positive margins (highest impact), and/or invasion of the seminal vesicles.	Strong
	Discuss three management options with patients with pN+ disease after an ePLND, based on nodal involvement characteristics: 1. Offer adjuvant ADT for node-positive (pN+). 2. Offer adjuvant ADT with additional radiotherapy. 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	Weak

Non-curative or palliative treatments in a first-line setting		
Localised disease		
Watchful waiting	Offer WW to asymptomatic patients not eligible for local curative treatment and those with a short life expectancy.	Strong
	While on WW, base the decision to start non-curative treatment on symptoms and disease progression.	Strong
Locally advanced disease		
Watchful waiting	Offer a deferred treatment policy using ADT monotherapy to M0 asymptomatic patients with a PSA-DT > twelve months, a PSA < 50 ng/mL and well differentiated tumour, who are unwilling or unable to receive any form of local treatment.	Strong
Metastatic disease in a first-line setting		
Symptomatic patients	In M1 symptomatic patients, offer immediate systemic treatment to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, and extra-skeletal metastasis).	Strong

Asymptomatic patients	In M1 asymptomatic patients, offer immediate systemic treatment to improve survival, defer progression to a symptomatic stage and prevent serious disease progression-related complications.	Strong
	In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side effects, provided the patient is closely monitored.	Weak
All M1 patients	Offer LHRH antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
	In M1 patients treated with a LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.	Weak
	Do not offer anti-androgen monotherapy for M1 disease.	Strong
	Offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for docetaxel.	Strong

	Offer castration combined with abiraterone acetate plus prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
	Offer castration alone, with or without an anti-androgen, to patients unfit for, or unwilling to consider, castration combined with docetaxel or abiraterone acetate plus prednisone.	Strong
M1 patients receiving Intermittent treatment	In asymptomatic M1 patients, only offer intermittent treatment to highly motivated men, with a major PSA response after the induction period.	Strong
	• In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment. • Stop treatment when the PSA level is < 4 ng/mL after six to seven months of treatment. • Resume treatment when the PSA level is > 10-20 ng/mL (or returned to the initial level of < 20 ng/mL).	Weak
	Do not use castration combined with any local treatment (RT/surgery) outside an investigational setting except for symptom control.	Strong

Guidelines for second-line and palliative treatments

Biochemical recurrence after treatment with curative intent		
Biochemical recurrence after radical prostatectomy (RP)	Offer AS and possibly delayed salvage RT (SRT) to patients with a biochemical recurrence and favourable prognostic factors (≤ pT3a, time to biochemical recurrence > three year, PSA-DT > twelve months, GS ≤ 7), who may not benefit from intervention.	Strong
	Treat patients with a PSA rise from the undetectable range with SRT. The total dose of SRT should be at least 66 Gy and should be given early (PSA < 0.5 ng/mL).	Strong
Biochemical recurrence after RT	Treat highly selected patients with localised PCa and a histologically proven local recurrence with salvage RP (SRP).	Weak
	Salvage RP should only be performed in experienced centres.	Strong
	Do not offer HIFU, cryosurgical ablation and salvage brachy-therapy to patients with proven local recurrence since it is still experimental.	Strong
Systemic salvage treatment	Do not offer ADT to M0 patients with a PSA-DT > twelve months.	Strong

Life-prolonging treatments of castration-resistant disease		
	Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing castration-resistant PCa (CRPC).	Strong
	Do not treat patients for non-metastatic CRPC outside of a clinical trial.	Strong
	Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
	Treat patients with mCRPC with life-prolonging agents. Base the choice of first-line treatment on the performance status (PS), symptoms, comorbidities, location and extent of disease, patient preference, and on the previous treatment for hormone-sensitive PCa (alphabetical order: abiraterone, docetaxel, enzalutamide, radium-223, sipuleucel-T).	Strong
Cytotoxic treatments of castration-resistant disease		
	Counsel, manage and treat patients with mCRPC in a multidisciplinary team.	Strong
	Offer patients with mCRPC who are candidates for cytotoxic therapy docetaxel with 75 mg/m^2 every three weeks.	Strong

	In patients with mCRPC and progression following docetaxel chemotherapy offer further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide and radium-223.	Strong
	Base second-line treatment decisions of mCRPC on pre-treatment PS, symptoms, patient preference, comorbidities and extent of disease.	Strong
Supportive care of castration-resistant disease		
	Offer bone protective agents to patients with mCRPC and skeletal metastases to prevent osseous complications.	Strong
	Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates.	Strong
	Treat painful bone metastases early on with palliative measures such as EBRT, and adequate use of analgesics.	Strong
	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.	Strong

Follow-up after treatment with curative intent

- After RP, PSA should be undetectable (< 0.1 ng/mL). A PSA of > 0.1 ng/mL after RP is a signal of residual prostate tumour tissue. After an undetectable PSA is obtained following RP, a PSA > 0.4 ng/mL and rising, best predicts further metastases.
- After RT, an increase in PSA > nadir + 2 ng/mL best predicts further metastases.
- Palpable nodules and increasing serum PSA are often signs of local recurrence.

Recommendations for follow-up	Strength rating
Routinely follow-up asymptomatic patients, by obtaining a disease-specific history and serum prostate-specific antigen (PSA) measurement. These should be performed at three, six and twelve months after treatment, then every six months until three years, and then annually.	Strong
During follow up, perform a systematic digital rectal examination (DRE) after surgery if unfavourable pathology (> pT3, pN1, Gleason ≥ 8).	Weak
During follow up, perform a systematic DRE after radiotherapy.	Strong
At recurrence, only image to detect local recurrence if it affects treatment planning.	Strong
Do not routinely offer bone scans and other imaging modalities to asymptomatic patients if there are no signs of biochemical relapse. In case patients have bone pain or other symptoms of possible progression, restaging should be considered irrespective of serum PSA level.	Strong

Recommendations for follow-up during hormonal treatment	Strength rating
Evaluate patients at three to six months after the initiation of treatment.	Strong
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients with stage M0 disease, schedule follow-up every six months. As a minimum requirement, include a disease-specific history, DRE and serum PSA determination in the diagnostic work-up.	Strong
In patients with stage M1 disease, schedule follow-up every three to six months. As a minimum requirement, include a disease-specific history, DRE, serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up. The testosterone level should be checked, especially during the first year.	Strong
Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, adapt/individualise follow up.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration resistant PCa (CRPC) requires a testosterone level < 50 ng/dL (< 1 mL/L).	Strong
Do not offer routine imaging to otherwise stable asymptomatic patients.	Strong

Quality of Life

Treating PCa can affect an individual both physically and mentally, as well as his close relations and his work or vocation. These multifaceted issues all have a bearing on his perception of 'quality of life (QoL)'. Prostate cancer care should not be reduced to focusing on the organ in isolation. Taking QoL into consideration relies on understanding the patient's wishes and preferences so that optimal treatment proposals can be formulated and discussed. There is clear evidence of unmet needs and ongoing support requirements for some men after diagnosis and treatment for PCa.

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-01-1), available to all members of the European Association of Urology at their website: http://www.uroweb.org/guidelines/.