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Guidance on Patient Consultation. Current Evidence for Prostate-Specific Antigen Screening in Healthy Men and Treatment Options for Men with Proven Localised Prostate Cancer

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Abstract The main objective of this review is to summarise, for primary and secondary care doctors, the management options and current supporting evidence for clinically localised prostate cancer. We review all aspects of management including current guidelines on early cancer detection and the importance of informed consent on PSA-based screening and assess the most common treatment options and the evidence for managing patients with low-, medium-, and high-risk disease.

Keywords Active surveillance · Erectile dysfunction · Localised prostate cancer · Prostate-specific antigen testing · Prostate-specific antigen screening · Radical prostatectomy

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Abbreviations

PCa	Prostate cancer
PSA	Prostate-specific antigen
EAU	European Urology Association
QoL	Quality of life
AS	Active surveillance
RT	Radiation therapy
RP	Radical prostatectomy
RCT	Randomised clinical trial
AUA	American Urological Association
NCCN	National Comprehensive Cancer Network
OS	Overall survival
DRE	Digital rectal examination
LE	Level of evidence
ASAP	Atypical small acinar proliferation
PIN	Prostatic intra-epithelial neoplasia
TRUS	Transrectal ultrasound
MR	Magnetic resonance
Gs	Gleason score
CT	Computer tomography
ED	Erectile dysfunction
WW	Watchful waiting
PCSS	Prostate cancer-specific survival
PCSM	Prostate cancer-specific mortality
DMFS	Distant metastasis-free survival
PSM	Positive surgical margins
BPFS	Biochemical progression free survival
eLND	Extended pelvic lymph node dissection
EBRT	External beam radiation therapy
LDR-BT	Low-dose rate brachytherapy
HDR-BT	High-dose rate brachytherapy
IMRT	Intensity-modulated radiation therapy
IGRT	Image guidance radiation therapy

SBRT	Stereotactic body radiation therapy
ADT	Androgen deprivation therapy
PLN	Pelvic lymph node
CSAP	Cryosurgery

Introduction

Prostate cancer (PCa) is the most common solid cancer in men in Europe, with an incidence rate that can reach 214 cases per 1000 men [1•]. The widespread access to early detection programmes for PCa and the associated lowering of the reference threshold of serum prostate-specific antigen (PSA) have driven a dramatic increase in the number of prostate biopsies, with an escalation of diagnoses of clinically localised PCa (up to 90 % of cases)[2] and associated downward stage migration effect [3•].

There remains lack of clarification on the systematic application of PCa screening, and there is disagreement on the use of PSA testing. Indeed, European Urology Association (EAU) guidelines confirm controversial scientific evidence to support the introduction of a population-based screening for the early detection of PCa in all men [1•] Some large studies have confirmed that an increased detection not only results in a reduction of PCa-specific mortality (PCSM) but also results in an overdiagnosis and overtreatment risk [4••]. On the other hand, the natural course of clinical localised PCa is mostly indolent, typically represented by slow tumour progression and reduced likelihood of future local and distant dissemination. Although technical advances are continually improving the results of surgical treatments and radiation therapy (RT), there has also been a focus on identifying clinically indolent tumours that are able to be managed with active surveillance (AS). The main aim of this approach is to limit risks of functional impairment, namely urinary incontinence and erectile dysfunction. In the presence of clinical localised PCa, asymptomatic patients that decide to undergo interventional treatment need to weight the benefits of treatment with the functional risks and effect on quality of life (QoL). However, understaging from prostate needle biopsies ranging between 19 and 57 %, when compared to radical prostatectomy (RP) specimen [5], indicate the further importance and difficulty of selecting the right therapy for the right patient at the right moment.

The purpose of this paper is to review current evidence for clinical practice with a focus on informed consent [6] capable of directing and informing asymptomatic men with localised PCa and helping avoid possible biases that general practitioner, urologists, radiation and medical oncologists could encounter.

Prostate Cancer Screening

The latest update of the randomised clinical trial (RCT) of prostate screening group of the Prostate, Lung and Colon Cancer (PLCO) screening [7] showed conflicts about whether routine screening for PCa results in decreased overall mortality. The recent update of the European Randomised Study of Screening for Prostate Cancer (ERSPC) RCT confirmed a substantial reduction in mortality attributable to testing of PSA and showed a substantially increased absolute effect at 13 years [4••]. However, it has also been suggested that 23–42 % of incidental cancers are overdiagnosed and the latest EAU guideline has not shown any current level 1 evidence to introduce widespread population-based screening programmes for early PCa detection in all men [1•].

Screening for PCa may advance diagnosis by at least 10 years [8], and a unanimous conclusion is that further quantification of harms and their reduction are still considered a prerequisite for the introduction of populated-based screening. Rather, early detection (opportunistic screening) should be offered to the well-informed men.

Opportunistic or case finding screening is intended when the decision to undergo early PSA testing should be shared between the patient and his physician outside from any organised screening programme [9]. Certain particular category risk should be informed on the pros and cons of PSA-based screening. The application of proper *decision aids* and *personalised*, *or individualised*, *risk information*, intended as information about the probability of future health outcomes for individual patient, have been shown to increase knowledge about PCa-screening [10], decrease participation in screening and reduce frequency of the uptake of PSA testing [11]. Increasing age, ethnic origin and heredity are the three well-established risk factor of PCa.

Increasing Risk Factor of Pca and Case Finding Identification

Age

Autopsy studies confirm that PCa has a long induction period and that many men have incipient lesions in their 20s and 30s [12]. The risk increases after the age of 50 in white men with no familiarity and after the age of 40 in men with a family history of PCa or Afro-Caribbeans and peaks at age 70–74 declining slightly subsequently. Life expectancy estimation, although challenging for some individuals, can be estimated using various tables/nomograms [3•].

The American Urological Association (AUA) does not recommend routine PSA screening in men aged 40–54 years old who are not at increased risk for the disease based on family history and race [3•].

A position paper of the EAU suggested a baseline PSA determination at age 40, on which the subsequent screening

interval may then be based [13]. A screening interval of 8 years might be enough in men with initial PSA levels <1 ng/ml. Even if about 80 % of men who reach age 80 have PCa, further PSA testing is not necessary in men >75 years and with a baseline PSA <3 ng/ml because of their very low risk of dying from PCa [1•].

The recently updated National Comprehensive Cancer Network (NCCN) guidelines [14•] indicate informed testing starting at age ≥45, with annual to biannual testing in those with a PSA above the age-specific median (0.7 ng/ml for men 40–49 years of age and 0.9 ng/ml for men 50–59 years). For those below the median, a retest at age ≥50 is recommended. The annual or biannual follow-up is recommended for all men with a PSA value above 1.0 ng/ml [14•].

Family History and Genetic Factor

In the presence of two or more first-line relatives, an increases risk of 5–11 times has been shown. If one first-line relative has the disease, the risk is at least doubled [15]. True hereditary PCa, distinct by three or more relatives affected or at least two relatives who have developed early-onset disease (<55 years of age), accounts for up to 9 % of men with PCa [16]. Up to date, known rare gene mutations [17] have been identified as being associated with increased risk of PCa. Even if these mutations can explain only 35 % of the familial risk [18], genetic variants and tests could offer future improvements to clinical practice.

Race, Ethnicity and Geography

African-American, African-Caribbean men are roughly 60 % and 60-fold more likely to develop PCa and 50 % and 12-fold more likely to die for PCa than, respectively, Caucasian and Chinese men [3•, 19]. However, Asiatic and African males living in their native countries have a low incidence of PCa. Japanese-Americans have an incidence rate 43 times higher than Japanese, and there is data indicating that migrants develop the high-risk pattern within one generation. Analysing the incidence of mortality, some differences between geographical regions have been identified as well. For instance, Spain and Italy have a relative risk of 2 and 1.5 times lower than Sweden [8, 19].

Other Risk Factors

Ionising and *ultraviolet radiation* from sun exposure and cadmium contact have been linked to PCa [20•]. *Trichomonas vaginalis* is the only certain pathogen found to correlate with PCa [21].

Among lifestyle habits, many studies confirmed that *smoking* is linked with higher risk of PCSM end recurrence and is strongly correlated with aggressive cancer [20•]. *Metabolic syndrome* is weakly associated with PCa, and among single components of the syndrome, only hypertension and waist circumference >102 cm were associated with a significantly greater risk of PCa, increasing it by 15 and 56 %, respectively [22]. In this process, dairy protein, red meat, coffee and dietary fat could be promoters, and several studies showed a small inverse correlation between PCa and physical activity [23].

The understanding of how diet affects PCa incidence and progression continues to develop, but it is suffice to say we are a long way from finding the 'miracle diet molecule' that cures or prevents cancer [24]. Among endogenous substances, *sexual hormones* do not seem to be involved in the carcinogenic process; in contrast, circulating levels of *insulin-like growth factor* showed a correlation with PCa [25].

Chemoprevention

Different RCT showed that *5-alfa reductase inhibitors* (5ARIs) reduces the overall cancer incidence risk, but mainly restricted to tumours with Gs <6, and these findings were not without controversy, namely the absence of effect on high-grade PCa and potential increase in incidence of high-risk tumours [26]. The Prostate Cancer Prevention Trial group (7- and 15-year follow-ups in healthy men under finasteride, PSA ≤3 mg/ml) showed 24.8 % overall cancer reduction with a 27 % increase of Gs ≥7 and no difference in 15-year overall survival (OS) [27]. Similarly, the REDUCE group (high-risk men on dutasteride with previous negative biopsy and PSA2.5 10 ng/ml, 4-year follow-up) showed an increase in Gs10 and no effect on Gs7 [28]. In conclusion, clinicians should keep in mind the PSA biopsy thresholds in patients receiving 5ARIs, since PSA maintains its predictive value but values are reduced by 50 % and no strong recommendation on cancer prevention related to the use of 5ARIs should be given [29]. A meta-analysis confirmed a 16–19 % reduction of lethal PCa in patients taking habitually *aspirin* [30].

Among other preventive dietary agents, neither *selenium* nor *vitamin D and E* supplements had beneficial effect, conversely the latter seems to increase PCa incidence [20•]. High intake of *lycopene*, an open-chain carotenoid found in tomato sauce, shows a potential (RR 0.89) effect although with very low evidence [1•, 20•].

Risks of PSA Testing

Among potential risks, the high rate of *false positives* (roughly 76 %) raises the suspicion of PCa and leads to *prostate biopsy*, a procedure that is not free of complications, including haematuria (10–84 %), rectal bleeding (1.3–45 %), haematospermia (1.1–93 %), infection, sepsis (1–4 %), acute urinary retention (0.2–0.7 %), lower urinary tract symptoms

(6–25 %), pain (18 %), erectile dysfunction (ED) (minimal and often transient) and mortality (0.2–1.3) [31].

Since most men will die from other causes before their cancer becomes symptomatic, *overdiagnosis and overtreatment* are significant concerns. Rates of overdiagnosis occur in roughly 40 % of all PCa detected through screening [3•], and up to 90 % of men with low PSA receive early intervention [32]. Overtreatment carries a significant risk of unavoidable side effects, which is the major adverse result of PCa screening [4••].

PCa Diagnosis and Clinical Staging

The main diagnostic tools include DRE, PSA and ultrasound-guided biopsy. Histologic examination is mandatory.

Digital Rectal Examination

Digital Rectal Examination (DRE) is the most sensitive method for the diagnosis of palpable prostatic abnormalities. In approximately 18 % of all patients, PCa is detected by a PCa-suggestive finding on DRE alone, regardless of the PSA level [1•]. However, it lacks specificity for PCa. A suspect DRE in patients with a PSA level of ≤2 ng/ml has a positive predictive value of 5–30 % [33].

Prostate-Specific Antigen Interpretation

Risk of PCa increases linearly with PSA increase. A PSA cutoff of 3–3.1 mg/l should be considered for World Health Organization-calibrated assays to achieve the same sensitivity (67–80 %) and specificity profile found with a cutoff of 4 mg/L in traditionally calibrated assays [34]. In order to improve the sensitivity, and avoid the loss of cancer diagnosis, a 2.5 ng/ml cutoff was recently recommended by the NCCN guidelines [14•]. However, an important study has highlighted the risk of PCa even in low levels of PSA [35].

The *free to total PSA* (*%fPSA*) may increase the diagnostic specificity by 15–20 %, and it is recommended with PSA values between 4.0 and 10 ng/ml. In a prospective multicentre trial, tumour was found on biopsy in 56 % of men with f/t PSA <0.10, but in only 8 % of men with f/t PSA >0.25 [36].

A single elevated PSA value should not lead to early alarmism, and a second test performed by the same assay should be repeated in 2–3 weeks [1•, 3•, 13].

Other Markers

Prostate health index (molecular isoform of the free PSA) and *four-kallikrein protein* [37, 38] appear to be more accurate and improve specificity in comparison to PSA-based assays, but are lacking validation.

Similarly, new urinary sediment markers obtained after prostatic massage, the *PCA3* and *TMPRSS2 with ERG* [39], offer improved specificity. Though already available on market, the former is not able to distinguish between low- and high-risk lesions. EU guidelines leave room for this score in the decision-making process in men with a negative first biopsy but persistent suspicion of PCa (positive follow-up biopsy shows a double PCA3-score) [1•].

Ultrasound-Guided Biopsy

In the suspicion of PCa and after assessing the potential risks/benefits, biological age, potential patient's comorbidity and therapeutic consequences, transrectal/transperineal ultrasound-guided biopsy represent the next diagnostic step [1•, 3•]. The standard care is represented by biopsy performed with 18G-needle with at least 10–12 (or more if prostatic volume >40 ml) laterally directed (as far posterior and lateral in the peripheral gland as possible) cores, under ultrasound-guided peri-prostatic block with prophylactic oral or intravenous quinolone antibiotics. In the suspicion of a urinary tract infection, biopsy should be postponed and urine cultured [1•, 3•, 14•]

Repeat Biopsy

Latest international guidelines advise repeat biopsy in case of rising and/or persistently elevated PSA, suspicious DRE (5–30 % risk of PCa), atypical small acinar proliferation (ASAP; 40 % risk) and extensive (multiple biopsy sites) prostatic intraepithelial neoplasia (PIN; 20–30 %) [1•, 3•, 13].

Imaging

Transrectal ultrasound (*TRUS*) is not recommended for routine use in staging, since only 60 % of PCa are detectable [1•, 13].

Multiparametric-magnetic resonance (*MR*) may improve prediction of pathological staging when combined with clinical data. Because of the low sensitivity to microscopic extracapsular extension, MR is not recommended in the local staging of low-risk PCa. In the absence of 3T, the endorectal coil at 1.5 T increases the accuracy by 15–20 % [40].

If clinical suspicion for PCa persists after a negative biopsy, multiparametric MRI may be applied since up to 21 % of PCa is located at the apical/anterior aspects of the prostate [41].

A TRUS- or direct MR-guided or image MR-US fusion targeted biopsy of the suspicious area can follow [1•, 3•, 13]. Targeted biopsies are several times more sensitive, although the false-negative rate is unknown. Therefore, targeted biopsy must always be accompanied by systematic biopsy and a negative MRI should not be used as a reason to defer biopsy [40].

Abdominal computer tomography (*CT*) *and MR* can be useful in the detection of node involvement in medium- to high-risk PCa (PSA >10 ng/ml, Gleason score [Gs] ≥8). Node involvement risk can be delineated by nomograms (Briganti's and Cagiannos's nomogram or Partin table) [42]. *Bone scan* should always be performed in symptomatic patients and recommended in asymptomatic with PSA >20 ng/ml or high-risk PCa [1•, 3•, 14•].

Treatment of Clinical Localised PCa

Low Risk (cT1-T2a, Gs ≤ 6 and PSA < 10 ng/ml)

Watchful Waiting

In presence of patients with reduced life expectancy (<10 years), age related or in presence comorbidity (Charlson score ≥2), watchful waiting (WW), intended as conservative/deferred/non curative management, could be an option [1•, 3•, 14•, 43••]. Treatment should be symptom and PCa progression related (e.g. palliative transurethral resection of the prostate in case of urethral obstruction or bleeding). The Geriatric-8 (G8) health status screening tool is highly recommended: 'fit' patients (G8 score >14) should be managed as the younger counterpart; other patients need a complete geriatric evaluation to evaluate possible reversibility of any impairment [44•].

Active Surveillance

In order to reduce risk of overtreatment, some clinical localised PCa could avoid or defer a curative treatment. Active surveillance (AS) represents a protocol-driven approach to surveillance management, and the rationale originates from early studies showing an 80–90 % rate of 20-year PCa-specific survival (PCSS) in low-risk patients [45]. The longest follow-up available (10 years, mean 6.8 years) (study selection: cT1c-T2a, PSA ≤10 ng/ml, Gs ≤6 (≤70 years) or ≤3+4 (>70 years)) showed a PCSM of 2.8 % [46••]. One third of the patients subsequently underwent radical treatment based on PSA doubling time <3 years (48 %), Gs progression on follow-up biopsies (27 %) or patients' choice (10 %). Other studies have showed a higher PCSM in patients with >15 years life expectancy and well/moderately differentiated PCa [47]; therefore, selection criteria for AS should be strict: clinically confined PCa (cT1-2), Gs ≤6, ≤3 positive biopsies, ≤50 % of each biopsy involved, PSA <10 ng/ml, PSA density <0.15 ng/ml/g [1•, 3•, 14•].

AS protocol is based on repeated DRE, PSA and biopsy. Early repeated confirmatory biopsy is an important part of the eligibility condition to exclude possible under-detection of Gs4, and targeted prostate biopsy (MR) may improve this stage [48].

Cancer progression is defined by Gs advance to ≥7 at re-biopsy; whereas PSA-DT and PSA progression have been lately questioned, the 'safety' of routine re-biopsies at 1- and 4-year intervals is recommended [1•, 3•, 49]. Though up to 18 % of patients voluntarily chose to abort AS in favour of active treatment, AS seems to be well tolerated with minimal effects on the QoL [50]. Main concerns of AS are related to the potential side effects due to repeated biopsies (infection and potential ED because of nerves damage) [51].

Radical Prostatectomy

The role of RP compared to WW in low-risk PCa showed mixed results in the few prospective RCT available. For instance, the SPCG-4 (695 patients, cT1-2N0M0, WW vs RP, median follow-up 12.8 years) showed an absolute 10-year PCSM reduction of 4.5 % in <65-year-old patients, but no evidence in the elderly (>70 years). However, RP was associated with increased distant metastasis-free survival (DMFS) among older men (RR, 0.68; $P=0.04$) [52]. On the other hand, the PIVOT trial (731 patients, cT1c-2cN0M0, PSA <50 ng/ml, <75 years, life expectancy >10 years, WW vs RP) did not demonstrate any advantage [43••].

However, the well-known risk of upgrading and upstaging at pathological analysis (up to 30–60 % in cT1c) [53] and the risk of disease progression of cT2a found to be 35–55 % after 5 years in studies [54] suggest that RP is a reasonable approach even in low-risk PCa. Intermediate/maximal nerve-sparing approach (bi-/monolateral) can also be offered with this staging in preoperatively potent patient. Among surgical approach, retropubic, laparoscopic and robot-assisted offer equivalent result in experienced hand (complication and positive surgical margins [PSM], but the latter grants decreased blood loss and transfusion rates and a positive trend in 1-year continence rate (89–100 % vs 80–97 %)) and erectile function recovery (55–81 % vs 26–63 %) [55]. Younger age at surgery and some modifications of the surgical technique (length of urethral stump, preservation of bladder neck, nerve-sparing procedure) showed a positive impact on continence recovery [1•, 56]. Extended pelvic lymph node dissection (eLND) has no current role in low-risk PCa [57].

Radiation Therapy

Due to significant technical advances, radiation therapy (RT) has become more effective and better tolerated during the last two decades. External beam RT (EBRT) and brachytherapy, applied either as low- (LDR-BT or 'seed implantation') or as high-dose (HDR-BT), are the main modalities. The gold standard EBRT is intensity-modulated RT (IMRT), which should be applied with some form of image guidance (IGRT). IMRT and IGRT allow the safe delivery of high doses (≥74 Gy) [58••, 59] demonstrated to be superior to lower-dose RT in

terms of BPFS [60]. The major difference of EBRT as compared to RP is its non-invasiveness and typically not requiring inpatient hospital stays.

Low-risk unfit or refusing AS can be treated equally effective by dose-escalated IMRT or LDR-BT as a monotherapy with a BPFS of 92–99 % after 7–10 years and DMFS of 99 % at 7 years, respectively [58••, 61]. Genitourinary late grade 3 toxicity after both approaches is <3 %, and generally, symptoms after high-dose IMRT appear to return towards baseline in the majority of patients [62•]. Gastrointestinal late toxicity can occur after high-dose IMRT, with grade 3 late events <1 % [58••]. LDR-BT offers a significant lower time commitment when compared to high-dose IMRT with normal dose per fraction (1.8–2 Gy) (1 day vs 7–8 weeks in total) [62•]. HDR-BT as a monotherapy might also be an option in experienced hands, but some concerns may remain regarding urethral late toxicity [63].

An even more recent advantage in the delivery of EBRT is stereotactic body RT (SBRT). Due to more precise patient positioning, commonly combined with improved IGRT, SBRT can apply higher doses per fraction (6,7-7,25 Gy; 'extreme hypofractionation') and thus significantly shorten the total treatment time (5–9 days) with equal BPFS and early/late toxicity as compared to other modalities [64]. The concomitant use of androgen deprivation treatment (ADT) or prophylactic RT of pelvic LN is not recommended for low-risk PCa. In the absence of RCT, several large observational studies did not show any difference between RT and RP, by means of PCSS and DMFS, in low-risk PCa [65–67].

Other Curative Options

Among new emerged minimally invasive techniques, whole gland cryosurgery (CSAP) and high-intensity focused ultrasound (HIFU) have gained some popularity, but lack long-term (>10 year) outcome results and should therefore only be currently considered in the research setting [1•].

The former consists of a TRUS-guided introduction of cryoneedles and consequent freezing (−40 °C) of the prostate. The 3rd-generation CSAP, suggested in patients with <40-ml gland, not fit for standard curative treatment and with a life expectancy >10, offers a 7-year BDFS of 61 % with ED (80 %) and urinary incontinence (4.4 %) among the most significant complications [68].

HIFU results in coagulative necrosis damage (65 °C) produced by transrectal release of ultrasound waves and provides BDFS of 76–85 % (6.4- and 4.5-year follow-up) and subsequent subvesical obstruction requiring operative correction (TURP or bladder-neck incision) (7.6–20 %), incontinence (3.1–6.4 %) and ED (55–70 %) are the main features [69, 70].

Intermediate Risk (cT2b-c or Gleason 7 or PSA 10–20 ng/ml)

Active Surveillance

It could be an option for patients with low life expectancy [1•, 3•, 14•].

Radical Prostatectomy

Stage pT2b could progress at 5 years in >70 % of cases [71], and RP could avoid this. Many large RCT reported a lower PCSM (up to 33 %), especially for a younger patient (<65 years or life expectancy >10 years) [43••, 52]. eLND should be performed in case of >5 % estimated risk for positive lymph node [57]. Role of maximal (intra/interfascial) nerve-sparing procedure should be carefully investigated (nomograms and MR), due to the possible risk of extracapsular involvement (cT2c or multiple ipsilateral Gs7) [1•, 3•, 14•].

Radiation Therapy

At this stage, a concomitant short-term ADT (3–6 months) should be recommended to reduce PCSM [72, 73]. This combination showed even a protective role for late toxicities [74]. However, careful attention should be paid in patients with coronary heart disease, due to increased risk of non-PCa-related deaths [75]. BPFS, DMFS and PCSM rates are 85, 94 and around 3 %, 7 years after high-dose IMRT with concomitant short-term ADT, respectively [58••].

BT as a monotherapy has no role in intermediate-risk PCa, but either LDR-BT or HDR-BT can be combined with EBRT which results in comparable if not even improved cancer control and comparable late toxicity to high-dose IMRT [76]. SBRT might be an option also for intermediate-risk disease [77].

In the presence of two negative RCT, the prophylactic RT of PLN must be regarded with caution [78, 79].

Other Interventional Treatment Options

CSAP and HIFU offer 68 % (7-year follow-up) [68] and 63–65 % (6.4- and 4.5-year follow-up) BDFS [69, 70].

High-Risk Localised (Gleason Score 8–10 or PSA >20 ng/ml)

Radical Prostatectomy

Although the risk of extracapsular involvement is high at this stage, the rate of clinically localised PCa accounts up to 26–31 % [1•, 41, 48]. Moreover, it has been shown that a downgrading occurs in 30 % on pathological specimen, leaving potential for RP with curative intent able to offer an enhanced BPFS (Gs ≤7, 56 % vs Gs 8–10, 27 %) [80]. eLND

should be always performed since a clear advantage over standard LND has been shown in term of BPFS [57, 81]. However, higher complication, namely lymphocoeles, deep venous thrombosis and pulmonary embolism could be expected [82••].

Because of a high PSA failure rate (ranged between 40 and 63 %, 24–39 % and 25 %, respectively, at 5 and 10 and 15 years) [1•, 3•], a multimodal approach should be considered. However, data available show good results offered by RP with CSS at 5, 10 and 15 years ranging between 93 and 97 %, 83–91 % and 71–78 %, respectively [1•].

Even if in some recent large observational study RP were associated with better PCSS than RT in younger and fitter patients with high-risk PCa [65, 66], the absence of high-quality RCT and direct comparison of RP and RP does not allow to establish any conclusion.

Radiotherapy

Long-term (2–3 years) concomitant ADT improves PCSS [83, 84]. Prophylactic RT of the PLN is controversial, but despite the presence of two negative RCT [78, 79], PLN should prophylactically be treated when the risk of nodal involvement based on nomograms reaches a certain level (e.g. a risk >15 %) [1•, 42, 57].

There is LE1 from two RCT that RT and long-term ADT improve PCSS in high-risk patients compared to ADT alone [85, 86], and these data must be compared to the randomised data on RP vs WW [52] instead of taking into account biased retrospective comparison between the two treatment.

Considerations and Conclusions

Opportunistic screening may be offered to well-informed patients, even if young, but further research is urgently needed on methods to reduce overdiagnosis preferably by avoiding unnecessary biopsy procedures. Primary and secondary care doctors should aim to minimise the effect of unnecessary routine screening where large numbers of men are screened, biopsied, and treated to the benefit of only a few patients.

An increase in early detection of low-risk indolent cancers should not result in unnecessary overtreatments, and careful patient selection and follow-up planning are required. In carefully selected patients, AS is an excellent and well-tolerated solution for low-risk PCa.

RP and RT offer cancer control in a young/fit patient with low-risk PCa, differing mainly in potential side-effect profiles, although both groups have reduced detrimental effects due to advances in technology and applied techniques. In the absence of RCT head-to-head comparisons of RP and RT, collective evidence support RP as initial treatment in improving PCSS outcomes in younger/fitter men with intermediate/high-risk PCa. Regarding a thorough medical assessment, older/unfitter men with intermediate- and high-risk PCa and <10-year survival are likely to fare as well, if not better, with first-line radiotherapy treatment.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Giovannalberto Pini, Dr. Pirus Ghadjar and Dr. Peter Wiklund each declare no potential conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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