EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis and local treatment with curative intent

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Abstract

Objective: To present a summary of the 2016 version of the European Association of Urology (EAU) guidelines on screening, diagnosis, and local treatment with curative intent of clinically localised prostate cancer.

Evidence acquisition: The Working Panel performed a literature review of the new data (2013-2015). The guidelines were updated and the levels of evidence and/or grades of recommendation were added based on a systematic review of the evidence

Evidence synthesis: BRCA2 mutations have been added as risk factors for early and aggressive disease. In addition to the Gleason score the 5-tiered 2014 ISUP grading system should now be provided. Systematic screening is still not recommended. Instead, an individual risk adapted strategy following a detailed discussion and taking into account the patient's wishes and life expectancy must be considered. An early PSA test, the use of a risk calculator or one of the promising biomarker tools are being investigated and might be able to limit the over-detection of insignificant PCa. Breaking the link between diagnosis and treatment may lower the over-treatment risk. A multiparametric MRI using standardised reporting cannot rule out systematic biopsy, but nested more robust within the diagnostic work-up, it has a key role in local staging. Active surveillance always needs to be discussed with very low-risk patients. The place of surgery in high-risk disease and the role of lymph node dissection have been clarified, as well as the management of node positive patients. Radiotherapy using dose-escalated intensity-modulated technology is a key treatment modality with recent improvement in outcome based on increased doses as well as combination with hormonal treatment. Moderate hypofractionation is safe, but long-term data are still lacking. High-dose-rate brachytherapy represents an interesting way to increase the delivered dose. Focal therapy remains experimental as convincing long term outcome results are still lacking, in particular for cryosurgery and high-intensity focused ultrasound.

Conclusion: The knowledge in the field of diagnosis, staging and treatment of localised prostate cancer is rapidly evolving. The 2016 EAU guidelines on PCa summarise the most recent findings and provide recommendations for clinical practice. These are the first EAU

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prostate cancer guidelines endorsed by the European Society for Radiotherapy and Oncology (ESTRO), and International Society of Geriatric Oncology (SIOG) and reflect the multidisciplinary nature of prostate cancer management. A full version is available at the EAU office and online at http://uroweb.org/guideline/prostate-cancer/.

Patient Summary: Prostate Cancer remains the most common cancer diagnosed in men in Europe (with the exception of skin cancers). Over the past years, in Northern and Western Europe, the number of men diagnosed with prostate cancer has been on the rise. This may be due to an increase in opportunistic screening, but also other factors may be involved (diet, sexual behaviour, exposure to ultraviolet radiation). The authors propose that men who are potential candidates for screening should be engaged in a discussion with their clinician (also involving their families/caregivers) so that an informed decision may be made, as part of an individualised risk-adapted approach.

Introduction

The last summary of the European Association of Urology (EAU) guidelines on prostate cancer (PCa) was published in 2013 [1]. This paper summarises the new insights/many changes that have occurred in the screening, diagnosis and treatment of localised PCa over the last 3 years and is based on annual structured literature searches and systematic review as a continuous process. Evidence levels and grade of recommendation have been formulated according to the general principles of evidence based medicine [2].

Prostate cancer remains the most common cancer in males in Europe (excluding skin cancer). While the incidence of autopsy-detected cancers is roughly the same in different parts of the world, the incidence of clinically diagnosed PCa varies widely, being highest in Northern and Western Europe (> 200 per 100,000 men) [3]. Besides the increased opportunistic screening with PSA, this is suggested to be a consequence of exogenous factors, such as diet, chronic inflammation, sexual behaviour, and exposure to ultraviolet radiation [4].

Metabolic syndrome has been linked with an increased risk of PCa [5], but there is insufficient evidence to recommend lifestyle changes or a modified diet to lower this risk. In hypogonadal men, testosterone therapy is not associated with an increased PCa risk [6]. No drugs or food supplements have been approved for PCa prevention.

Apart from age and African-American origin, family history of PCa (both paternal and maternal [7]) is a well-established risk factor. If one first-degree relative has PCa, the risk is at least doubled. It increases by 5 – 11 times when two or more first-line relatives are affected [8]. About 9% of men with PCa have truly hereditary disease, which is associated with an onset six to seven years earlier than spontaneous cases, but the biology does not differ. The only exception are carriers of the rare BRCA2 germline abnormality, who seem to have an increased risk of early-onset PCa with aggressive behaviour [9-11].

Classification

The 2009 TNM classification for staging of PCa and the EAU risk group classification are recommended (Table 1). The latter classification is based on the grouping of patients with a similar risk of biochemical recurrence (BCR) after local treatment.

Table 1: EAU risk groups for biochemical recurrence of localised and locally advanced prostate Cancer

Low-risk	Intermediate-risk	High-risk	
Definition			
PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; PSA = prostate-specific antigen.

The ISUP 2005 modified Gleason score (GS) is the recommended PCa grading system. The biopsy GS consists of the Gleason grade of the most extensive pattern plus the highest grade, regardless of its extent. In radical prostatectomy (RP) specimens, the GS is determined differently: a pattern comprising ≤ 5% of the cancer volume is not incorporated in the GS but its proportion should be reported separately if it is grade 4 or 5.

The 2014 ISUP Gleason Grading Conference on Cleason Grading of Prostate Cancer [12] adopted the concept of grade groups of PCa, in order to align PCa grading with the grading of other carcinomas. Furthermore, it eliminates the anomaly that the most highly differentiated PCas have a GS 6 and highlights the clinical differences between GS 7 (3 + 4) and 7 (4 + 3) (Table 2).

Table 2: International Society of Urological Pathology 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

Grade groups can now be reported in addition to the overall or global Gleason score of a prostate biopsy or radical prostatectomy

Screening and early detection

Screening for PCa remains one of the most controversial topics in the urological literature. A Cochrane review [13] suggests that PSA screening is associated with an increased diagnosis rate (RR: 1.3; 95% CI: 1.02-1.65) and the detection of more localised (RR: 1.79; 95% CI: 1.19-2.70) and less advanced disease (T3-4, N1, M1) (RR: 0.80; 95% CI: 0.73-0.87). However neither overall survival (OS) (RR: 1.00; 95% CI: 0.96-1.03) nor cancer-specific survival (CSS) benefits were observed (RR: 1.00; 95% CI: 0.86-1.17). Moreover, screening was associated with over-diagnosis and over-treatment. All these considerations have led to a strong recommendation against systematic population-based screening in Europe and the USA. And yet, the European Randomized Study of (population-based) Screening for Prostate Cancer (ERSPC) showed a reduction in PCa mortality in the screening arm (RR: 0.8; 95% CI: 0.70-1.03) after a median follow-up of 9 years. Updated results from the ERSPC at 13 years of follow-up showed an unchanged cancer-specific mortality reduction 0.79 (0.69-0.91) [14], but the number-needed-to-screen (n=781) and to treat (n=27) to avoid one death from PCa decreased, and is now below the number-needed-to-screen in breast cancer trials [15] (Table 3). Furthermore, the uptake of the 2012 USPSTF recommendations against PSA testing has been associated with a substantial number of men with aggressive disease being missed [16]. Finally, a comparison of systematic and opportunistic screening suggested over-diagnosis and mortality reduction by systematic screening versus a higher over-diagnosis with at best a marginal survival benefit after opportunistic screening [17].

Table 3: Follow-up data from the ERSPC study [14]

Years of follow-up	Number needed to screen*	Number needed to treat*
9	1,410	48
11	979	35
13	781	27

* Number of men needed to screen or treat in order to avoid the death of disease of one man.
ERSPC = European Randomized Study of Screening.

Targeting men at higher risk of PCa might reduce the number of unnecessary biopsies. These include men above 50 years of age, or above 45 for African-American men or those with a family history of PCa. In addition, men with a PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [18, 19] are at increased risk of PCa metastasis or death several decades later. Risk calculators developed from cohort studies may also be useful in reducing the number of unnecessary biopsies. None have clearly shown superiority over another or can be considered as optimal [20].

Optimal follow-up intervals for PSA testing and digital rectal examination (DRE) are unknown. A 2-year interval for men at increased risk based on PSA level is reasonable, while it could be extended to up to 8-years for those not at risk. The age at which to stop PSA testing should be based on an individual's life expectancy where co-morbidity is at least as important as age [21]. Men who have less than a 15-year life expectancy are unlikely to benefit.

Application of all the currently available tools will still not rule out over-diagnosis. Breaking the link between diagnosis and active treatment is the only way to decrease the risk of over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it (Table 4).

Table 4: Guidelines for screening and early detection

Recommendation	LE	GR
Do not subject men to PSA testing without counselling them on the potential risks and benefits.	3	B
Offer an individualised risk-adapted strategy for early detection to a well-informed man with a good performance status and a life-expectancy of at least 10-15 years.	3	B
Offer PSA testing in 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	2b	A

• 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		
Offer a risk-adapted strategy (based on initial PSA level), with follow-up intervals of 2 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 8 years in those not at risk.	3	C
Decide on the age at which early diagnosis of PCa should be stopped based on life expectancy and performance status; men who have a life-expectancy of < 15-years are unlikely to benefit.	3	A

PCa = prostate cancer; PSA = prostate-specific antigen.

Diagnosis

Prostate cancer is usually suspected on the basis of digital rectal exam (DRE) and/or an elevated PSA. Definitive diagnosis depends on histopathological verification. Abnormal DRE is an indication for biopsy, but as an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS). PSA is a continuous parameter, with higher levels indicating greater likelihood of PCa, precluding an optimal PSA threshold for detecting non-palpable but clinically significant PCa. A minor PSA elevation alone should be confirmed after a few weeks under standardised conditions (i.e., no ejaculation, manipulations, and urinary tract infections) in the same laboratory before considering a biopsy. The empiric use of antibiotics to lower PSA in an asymptomatic patient is not recommended [22].

Free/total (f/t) PSA ratio stratifies the risk of PCa in men with 4-10 ng/mL total PSA and a previous negative biopsy but may be affected by several pre-analytical and clinical factors (e.g. instability of free PSA at 4°C and room temperature, variable assay characteristics, and large concomitant benign prostatic hyperplasia [BPH]). Novel assays for risk stratification measuring a panel of kallikreins including the Prostate Health Index (PHI) test, and the four kallikrein (4K) score test are developed to reduce the number of unnecessary biopsies in men with a PSA between 2-10 ng/mL. Prospective multicentre studies demonstrated that both tests out-performed f/t PSA for PCa detection [23, 24]. Nevertheless a formal comparison of these new tests is lacking.

Prostate biopsy

Transrectal ultrasound (TRUS)-guided biopsy using an 18G biopsy needle and a periprostatic block is the standard of care. When the same number of cores are taken, both transrectal and transperineal approaches have comparable detection rates [25, 26].

Ten to twelve core biopsies should be taken from the peripheral gland, bilateral from apex to base, as far posterior and lateral as possible. Additional cores should be obtained from DRE/TRUS suspicious areas. Oral or intravenous quinolones remain standard prophylactic antibiotics, in spite of the increasing resistance to quinolones, which is associated with a rise in severe and potentially lethal infectious complications [27]. Other biopsy complications include haematospermia (37%), heamaturia lasting more than 1 day (14.5%), rectal bleeding lasting < 2 days (2.2%). Each biopsy site should be reported individually, including type of carcinoma, its location, the ISUP 2005 GS and extent. ISUP 2014 grade should be given as a global grade, taking into account the Gleason grade(s) of cancer foci in all biopsy sites. If identified, intraductal carcinoma, lymphovascular invasion, perineural invasion and extraprostatic extension must each be reported.

Following an initial negative biopsy, the indications for repeat biopsy are summarised in Table 5.

Table 5: Indications for re-biopsy after a negative biopsy and the associated risk to find a prostate cancer

	Associated PCa risk
Rising and/or persistently elevated PSA	
Suspicious DRE	5-30%
Atypical small acinar proliferation (i.e., atypical glands suspicious for cancer)	40%
Extensive (multiple biopsy sites, i.e., ≥ 3) high grade prostatic intraepithelial neoplasia (HGPIN)	~ 30%
Few atypical glands immediately adjacent to high grade PIN (i.e., PINATYP)	50%
Intraductal carcinoma as a solitary finding	> 90% (mainly high-grade PCa)
Positive multiparametric MRI	34 – 68%

Many single-centre studies suggest that multiparametric MRI (mpMRI) can reliably detect aggressive tumours with a negative (NPV) and positive predictive value (PPV) ranging from 63 to 98% and from 34 to 68%, respectively [28]. The combination of systematic and targeted biopsies (MRI-Tbx) may also better predict the final GS [29]. As a result, some authors proposed performing systematic mpMRI before prostate biopsy [30, 31]. One meta-analysis suggested that MRI-Tbx had a higher detection rate of clinically significant PCa compared to TRUS biopsy (sensitivity 0.91 vs. 0.76) and a lower rate of detection of insignificant PCa (sensitivity 0.44 vs. 0.83). However this benefit was restricted to the repeat biopsy subgroup [32]. Three more recent RCTs restricted to the initial biopsy, yielded contradictory results regarding the added value of MRI-Tbx combined with systematic biopsies [33, 34]. Major limitations of mpMRI are its inter-observer variability and the heterogeneity in definitions of positive and negative examinations. The first version of the Prostate Imaging Reporting and DataSystem (PIRADS) scoring system did not improve inter-observer variability as compared to subjective scoring [35]. An updated version (PIRADS V2) needs to be evaluated further [36].

Staging of prostate cancer

The decision to proceed with further staging work-up is guided by which treatment options are available taking into account the patient's preference and comorbidity. A summary of the guidelines is presented in Table 6.

Table 6: Guidelines for staging of prostate cancer

Any risk group staging	LE	GR
Do not use CT and TRUS for local staging.	2a	A

Low-risk localised PCa	LE	GR
Do not use additional imaging for staging purposes.	2a	A

Intermediate-risk PCa	LE	GR

In predominantly Gleason pattern 4, metastatic screening, include at least a cross-sectional abdominopelvic imaging and a CT/MRI and bone-scan for staging purposes.	2a	A*
In predominantly Gleason pattern 4, use prostate mpMRI for local staging and metastatic screening.	2b	A

High-risk localised PCa/ High-risk locally advanced PCa	LE	GR
Use prostate mpMRI for local staging.	2b	A
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan.	2a	A

CT = computed tomography; mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PET = positron emission tomography; TRUS = transrectal ultrasound.

Primary local treatment

Management decisions should be made after all options have been discussed in a multidisciplinary team including urologists, radiation oncologists, medical oncologists, pathologists and radiologists, and after the balance of benefits and side effects of each treatment modality has been considered together with the patient.

Active Surveillance and Watchful Waiting

Active surveillance (AS) aims to reduce over-treatment in men with very-low risk PCa, without compromising opportunities for cure, while watchful waiting (WW) is a conservative management for frail patients until the possible development of clinical progression, necessitating symptomatic treatment. The major differences between these 2 modalities are detailed in Table 7.

Table 7: Definitions of active surveillance and watchful waiting

	Active surveillance (AS)	Watchful waiting (WW)
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	> 10 years	< 10 years
Aim	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity

Comments	Only for low-risk patients	Can apply to patients with all stages

DRE = digital rectal examination; PSA = prostate-specific antigen; mpMRI = multiparametric magnetic resonance imaging.

Mortality from untreated screen-detected PCa in patients with GS 5-7 can be as low as 7% at 15 years follow-up [37]. A randomised trial was unable to show an OS and CSS difference at 10 years between RP or WW in 731 men with screen-detected clinically organ-confined PCa [38]. Only patients with intermediate risk or with a PSA > 10 ng/mL had a significant OS benefit from RP (HR: 0.69. 95% CI: 0.49-0.98) and 0.67 95% CI: 0.48-0.94) respectively. A population based analysis of 19,639 patients aged > 65 years who were not given curative treatment found that in men having a Charlson Comorbidity Index score > 2, tumour aggressiveness had little impact on OS at 10 years [39]. These data highlight the potential role of WW in some patients with an individual life expectancy of less than 10 years.

A systematic review has summarised the available data on AS [40]. There is considerable heterogeneity between studies regarding patient selection, follow-up policies and when active treatment should be instigated. Selection criteria for AS include: clinical T1c or T2a, PSA < 10 ng/mL and PSA density < 0.15 ng/mL/cc (even if still controversial [41]), < 2 - 3 positive cores with < 50% cancer involvement of every positive core, and GS 6. Men with extraprostatic extension or lymphovascular invasion are exclusion criteria for AS [42]. Re-biopsy to exclude Gleason sampling error is considered important, [41] and mpMRI combined with targeted prostate biopsy demonstrated additional value in reclassification to high-grade PCa [43]. Its major role is furthermore based on its high NPV value for upgrading and to exclude anterior prostate lesions [43]. Follow-up in AS is based on repeat biopsy, [41] serial PSA measurements and DRE, but the optimal schedule remains unclear. Strategies how to incorporate mpMRI within this follow-up are evolving, but are not established yet. The decision to switch to active treatment is based on a change in the inclusion criteria (T-stage and biopsy results). The use of a PSA change (especially a PSA-DT < 3 years) remains contentious based on its weak link with grade progression. Active treatment may also be triggered upon a patient's request [44].

Radical Prostatectomy

The goal of RP is eradication of PCa, while preserving continence and, whenever possible, potency. It is the only treatment for localised PCa showing a benefit for OS and CSS, compared with WW. Patients should not be denied this procedure on the grounds of age alone [21] provided they have at least 10 years of life expectancy and are aware that increasing age is linked to increased incontinence risk. Nerve-sparing RP can be performed safely in most men with localised PCa. High risk of extracapsular extension, such as locally advanced disease or any GS > 7 are usual contraindications for a nerve-sparing approach. An externally validated nomogram predicting side-specific extraprostatic extension can help guide decision-making [45]. mpMRI may be helpful for selecting a nerve-sparing approach as it has good specificity (0.91 [95% CI: 0.88-0.93]) but low sensitivity (0.57 [95% CI: 0.49-0.64]) for detecting microscopic pT3a stages [46]. But the experience of the radiologist remains of paramount importance.

Lower rates of positive surgical margins for high-volume surgeons suggest that experience and careful attention to surgical details, can improve surgical cancer control [47] and lower complication rates.

There is still no evidence that one surgical approach is better than another (open, laparoscopic or robotic), as highlighted in a formal systematic review. Robot-assisted prostatectomy (RALP) is associated with lower perioperative morbidity and a reduced positive margin rate compared with laparoscopic prostatectomy, although there is considerable methodological uncertainty. No real differences exist in cancer-related-, continence- or erectile function outcomes [48].

Pelvic lymph node dissection

The individual risk of finding positive lymph nodes can be estimated using pre-operative nomograms such as the Briganti nomogram, which has been externally validated [49]. A risk of nodal metastases over 5% is an indication to perform an extended pelvic lymph node dissection (ePLND). This includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, the nodes medial and lateral to the internal iliac artery, and the nodes overlying the common iliac artery and vein up to the ureteral crossing. It is recommended that for each region the nodes should be sent separately for pathologic analysis. With this template, 75% of

all anatomical landing sites are cleared, resulting in a better staging accuracy as compared to a limited pelvic lymph node dissection (lPLND), but at the cost of higher complication rates (19.8% vs. 8.2%), mainly related to significant lymphoceles [50].

In men with positive pelvic nodes (pN+) PCa, early adjuvant ADT has been shown to achieve a 10-year CSS rate of 80% [51]. Furthermore, improving local control with pelvic radiotherapy combined with ADT appeared to be beneficial in pN1 PCa patients treated with an ePLND. Men with minimal-volume nodal disease (< 3 lymph nodes) and GS 7-10 and pT3-4 or positive margins as well as men with 3-4 positive nodes were more likely to benefit from combined ADT and RT after surgery [52].

Low-risk PCa: The decision to offer RP should be based upon the probabilities of clinical progression, side effects and potential survival benefit. No lymph node dissection is needed.

Intermediate-risk, localised PCa: Data from SPCG-4 [53] and a preplanned subgroup analysis (PIVOT) [36] highlighted the benefit of RP compared with WW. The risk of having positive nodes is 3.7-20.1% [49]. An ePLND should be performed if the estimated risk for pN+ exceeds 5% [49]. In all other cases, nodal dissection can be omitted, while accepting a low risk of missing positive nodes.

High-risk and locally advanced PCa: These patients are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Provided that the tumour is not fixed, and not invading the urethral sphincter, RP combined with an ePLND is a reasonable first step in a multimodal approach. The estimated risk for pN+ is 15-40% [49]. Regarding high-risk PCa patients treated with a multimodal approach, those with a GS 8-10 prostate confined lesion have a good prognosis after RP. In addition frequent downgrading exists between the biopsy and the specimen GS [54]. At 10- and 15-years follow-up the CSS is up to 88% and 66%, respectively [55, 56]. A PSA > 20 ng/mL is associated with a CSS at 10 and 15 years ranging between 83-91% and 71-85%, respectively [55 - 57]. Surgery has traditionally been discouraged for cT3N0 PCa, mainly because of the increased risk of positive margins and lymph node metastases and/or distant relapse. However, retrospective case series demonstrated a CSS at 10- and 15-years between 85-92% and 62-84% respectively, while 10-year OS ranged between 76-77% [58]. The overall heterogeneity of this high-risk group has been highlighted by a large retrospective multicenter cohort of 1360

high-risk patients treated with RP in a multimodal approach [58]. At 10 years, a 91.3% CSS was observed. CSS was 95% for those having only 1 risk factor (i.e. GS > 7 or cT > cT2 or PSA > 20 ng/mL), 88% for those having a cT3-4 and a PSA > 20 ng/mL, and reduced to 79% if all 3 risk factors were present.

Side effects of radical prostatectomy

Post-operative incontinence and ED are common problems following radical prostatectomy. There is no major difference based on the surgical approach with an overall continence rate between 89-100% when a robotic procedure was conducted compared with 80-97% for the open retropubic approach [59].

Recently, a prospective, controlled, non-randomised trial of patients treated in 14 centres was published. At 12 months after robotic surgery, 21.3% were incontinent, as were 20.2% after open RP. The adjusted OR was 1.08 (95% CI: 0.87-1.34). Erectile dysfunction was observed in 70.4% after robotic and 74.7% after open RP. The adjusted OR was 0.81 (95% CI: 0.66-0.98) [60].

Definitive Radiotherapy

Dose-escalated Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for external beam radiotherapy (EBRT) as it is associated with less toxicity compared with 3D conformal (3D-CRT) techniques [61]. However, whatever the technique and their degree of sophistication, quality assurance plays a major role in the planning and delivery of RT

Randomised studies have shown that escalating the dose into the 74-80 Gy range leads to a significant improvement in 5-year biochemical disease-free survival [62-65]. In men with intermediate- or high-risk PCa there is also evidence to support an OS benefit from a non-randomised but well conducted propensity matched retrospective analysis covering a total of 42,481 patients [66].

Biological modeling suggests that prostate cancer may be sensitive to an increased dose per fraction resulting in the investigation in randomised trials of hypofractionation (HFX). HFX delivered with fewer treatments can increase the convenience for the patient and lower costs for the health care system.

A systematic review concludes that studies investigating the efficacy of moderate HFX (2.5 - 4 Gy/fx) delivered with conventional 3D-CRT/IMRT have sufficient follow-up to

support the safety of this therapy, but long-term efficacy data are still lacking [67]. HFX requires meticulous quality assurance, excellent image guidance and close attention to organ at risk dose-constraints to minimise the long term toxicity risk. Extreme HFX (5-10 Gy/fx) where radiation is delivered in 5-7 fractions should still be considered as investigational.

Low-risk PCa: This patient category should be offered dose-escalated IMRT (74-78 Gy) without ADT.

Intermediate-risk PCa: Patients suitable for ADT should be given combined dose-escalated IMRT (76-78 Gy) with short-term ADT (4-6 months) [68]. For patients unsuitable for ADT (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT at a dose of 76-80 Gy or a combination of IMRT and brachytherapy.

Localised high-risk PCa: The high risk of relapse outside the irradiated volume makes it mandatory to use a combined modality approach, consisting of dose-escalated IMRT, possibly including the pelvic lymphatics and long-term ADT. The duration of ADT has to take into account performance status, comorbidities, and the number of poor prognostic factors.

Locally advanced PCa: T3-4 N0, M0: The standard of care is IMRT combined with long term ADT, as it results in better OS [69-71]. The combination is clearly better than EBRT or ADT monotherapy [72]. In both high-risk localised and locally advanced disease, upfront combination with docetaxel only improves relapse free survival, with no survival benefit at 9 years [73].

Lymph node irradiation

In men with cN0 PCa, randomised trials have failed to show a benefit from prophylactic pelvic nodal irradiation (46-50 Gy) in high-risk cases [74]. In men with cN1 or pN1 the outcome of radiotherapy alone is poor, and these patients should receive RT plus long-term ADT, as shown by the STAMPEDE trial where the use of radiotherapy improved failure-free survival in men with N+ PCa [75].

Post-operative EBRT after RP

Extra-capsular invasion and positive surgical margins are associated with a risk of local recurrence and progression. Adjuvant radiotherapy is associated at least with improved biochemical progression-free survival in 3 randomised trials [76-78] although only SWOG 8794 [78] suggested improved OS. Thus, for patients classified as pT3 pN0 with a high risk of local failure due to positive margins (highest impact), pT3a or pT3b with a post-operative PSA < 0.1 ng/mL, two options can be offered in the framework of informed consent: either immediate EBRT to the surgical bed after recovery of urinary function, or monitoring followed by early salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng/mL [79].

Side effects of Definitive Radiotherapy

The Memorial Sloan-Kettering Cancer Center group has reported data on late toxicity from their experience in 1571 patients with T1-T3 disease treated with either 3D-CRT or IMRT at doses of between 66 Gy and 81 Gy, with a median follow-up of 10 years [61]. The use of IMRT significantly reduced the risk of late grade 2 or higher gastrointestinal (GI) toxicity to 5% compared to 13% with 3D-CRT. The incidence of grade 2 or higher late genito-urinary (GU) toxicity was 20% in patients treated with 81 Gy IMRT vs. 12% with lower doses. The overall incidences of late grade 3 toxicity were 1% and 3% for GI and GU toxicity respectively.

Systematic review and meta-analysis of observational studies comparing patients exposed or unexposed to EBRT in the course of treatment for prostate cancer demonstrate an increased risk of developing second cancers for bladder (OR 1.39, 95% CI 1.12-1.71), colorectal (OR 1.68, 95% CI 1.33-2.12) and rectum (OR 1.62, 95% CI 1.26-2.08) with similar risks over lag times of 5 and 10 years. Absolute risks over 10 years are small (1-4%) but should be discussed with younger men in particular [80].

Low-dose rate (LDR) brachytherapy uses permanent radioactive seeds implanted into the prostate and is an option in those with low-risk disease and selected cases with intermediate-risk disease (low volume Gleason 3+4), prostate volume of < 50 cm^3 and an IPSS ≤ 12 [81]. Up to 85% relapse-free survival at 10 years is demonstrated [82]. LDR as a boost with EBRT can be used to dose escalate radiation in intermediate and high-risk patients. Although seen as a low impact treatment modality some patients experience significant urinary complications following implantation, such as urinary retention (1.5-22%), need for

post-implantation TURP (8.7% of cases), and urinary incontinence (0-19%) [83]. Previous TURP for BPH increases the risk of post-implantation incontinence and urinary morbidity. Erectile dysfunction develops in about 40% of patients after 3-5 years

High-dose rate (HDR) brachytherapy uses a radioactive source temporarily introduced into the prostate to deliver radiation. HDR brachytherapy can be delivered in single or multiple fractions and is often combined with EBRT of at least 45 Gy as a method of dose escalation in intermediate or high-risk PCa. Quality-of-life changes are similar to high-dose EBRT alone [84]. HDR brachytherapy as monotherapy has been pioneered in a small number of centres with low published toxicity and high biochemical control rates, but currently mature data is not available on the optimal treatment schedule [85].

Alternative local treatment options

Besides RP, EBRT and brachytherapy, other modalities have emerged as therapeutic options in patients with clinically localised PCa. However patients with a life expectancy > 10 years should be fully informed that there are limited data on the long-term outcome for cancer control beyond 10 years. Recently, focal therapy has been developed, with the aim to ablate tumours selectively whilst sparing the neurovascular bundles, sphincter and urethra. Based on the available data [86], it should still be considered as fully experimental.

Cryosurgery might be considered for patients with an organ-confined PCa or minimal tumour extension beyond the prostate, prostate volumes < 40 mL, PSA < 20 ng/mL, and GS of < 7.

A systematic review compared Cryotherapy vs. RP and EBRT [86]. Data from 3995 patients across 19 studies were included. In the short-term, there was conflicting evidence relating to cancer-specific outcomes. The 1-year disease-free survival was worse for cryotherapy than for either EBRT or RP. None of the other cancer-specific outcomes including OS, showed any significant differences. The high risk of bias across studies precludes any clear conclusions.

High-intensity focused ultrasound of the prostate (HIFU) has been compared in a systematic review [86] to RP and EBRT as primary treatment for localised PCa. Data from 4000 patients across 21 studies were included. HIFU had a significantly worse disease-free

survival at 1 year compared to EBRT. The differences were no longer significant at 3 years. The biochemical result was in contrast to OS at 4 years, which was higher when using HIFU. The quality of the evidence was poor, due to high risks of bias across studies precluding any clear conclusion.

The overall PCa guidelines are summarised in Table 8.

Table 8: Summary of the main findings regarding treatment of non-metastatic PCa

Recommendation	LE	GR
Management decisions should be made after all treatments have been discussed in a multidisciplinary team	4	A*
Offer RP to patients with low- and intermediate-risk PCa and a life expectancy > 10 years,	1b	A
Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extracapsular disease (T1c, GS < 7 and PSA < 10 ng/mL, or refer to Partin tables/nomograms).	2b	B
In intermediate- and high-risk disease, use mpMRI as a decision tool to select patients for nerve-sparing procedures	2b	B
Offer RP in a multimodality setting to patients with high-risk localised PCa and a life expectancy of > 10 years.	2a	A
Offer RP in a multimodality setting to selected patients with locally advanced (cT3a) PCa, and a life expectancy > 10 years.	2b	B
Offer RP in a multimodality setting to highly selected patients with locally advanced PCa (cT3b-T4 N0 or any T N1).	3	C
Do not offer NHT before RP.	1a	A
Do not offer adjuvant HT for pN0.	1a	A
Offer adjuvant ADT for node-positive (pN+).	1b	A
Offer EBRT using IMRT to all risk groups	2a	A
In patients with low-risk PCa, without a previous TURP, with a good IPSS and a prostate volume of < 50ml, offer LDR brachytherapy	2a	A
In low risk PCa, use a total dose of 74 to 78 Gy	1a	A
In intermediate- risk PCa use a total dose of 76-78 Gy, in combination with short-term ADT (4-6 mo).	1b	A
In patients with high-risk localised PCa, use a total dose of 76-78 Gy in combination with long-term ADT (2-3 yr).	1b	A
In patients with locally advanced cN0 PCa, offer radiotherapy in combination with long-term ADT (2-3 yr).	1a	A

In patients with cN1 PCa offer pelvic external irradiation in combination with immediate long-term ADT.	2b	B
Offer adjuvant ADT for pN1 after ePLND.	1b	A
Discuss adjuvant ADT with additional radiotherapy for pN1 after ePLND	2b	A
Offer observation (expectant management) for pN1 after eLND when ≤ 2 nodes show microscopic involvement with a PSA < 0.1 ng/mL and absence of extranodal extension	2b	B
In patients with pT3N0M0 PCa and an undetectable PSA following RP, discuss adjuvant EBRT because it improves at least biochemical-free survival	1a	A
Inform patients with pT3N0M0 PCa and an undetectable PSA following RP about salvage irradiation as an alternative to adjuvant irradiation when PSA increases	2b	A
Only offer cryotherapy and HIFU within a clinical trial	3	B
Do not offer focal therapy of the prostate outside a clinical trial	3	A

ADT = androgen-deprivation therapy; AS = active surveillance; DFS = disease-free survival; EBRT = external beam radiotherapy; ePLND = extended lymph node dissection; GS = Gleason score; HIFU = high-intensity focused ultrasound; HT = hormone therapy; IPSS = International Prostate Symptom Score; mpMRI = multiparametric magnetic resonance imaging; NHT = neoadjuvant hormonal therapy; OS = overall survival; PCa = prostate cancer; PSA = prostate-specific antigen; RP = radical prostatectomy; TURP = .transurethral resection of prostate.

Summary

The present text represents a summary of the 2016 EAU Prostate cancer guidelines. For more detailed information and a full list of references, refer to the full-text version (ISBN 978–90–79754–71–7), which are available at the EAU Web site (http://uroweb.org/guideline/prostate-cancer/).

BIBLIOGRAPHY

1. Heidenreich A, *et al*. EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent - Update 2013. Eur Urol. 2014 65: 124.

2. Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2009). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.

3. Arnold, M., *et al.* Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. Eur J Cancer, 2015. 51: 1164.

4. Leitzmann, M.F., *et al.* Risk factors for the onset of prostatic cancer: age, location, and behavioural correlates. Clin Epidemiol, 2012. 4: 1.

5. Esposito, K., *et al.* Effect of metabolic syndrome and its components on prostate cancer risk: metaanalysis. J Endocrinol Invest, 2013. 36: 132.22

6. Haider, A., *et al.* Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. J Urol, 2015. 193: 80.

7. Albright, F., *et al.* Prostate cancer risk prediction based on complete prostate cancer family history. Prostate, 2015. 75: 39011.

8. Hemminki, K. Familial risk and familial survival in prostate cancer. World J Urol, 2012. 30: 143.

9. Castro, E, *et al*. Effect of BRCA Mutations on Metastatic Relapse and Cause-specific Survival After Radical Treatment for Localised Prostate Cancer. Eur Urol, 2015. 68: 186.

10. Castro, E, *et al*. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer J Clin Oncol, 2013. 31: 1748.

11. Bancroft, EK, *et al*. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. Eur Urol, 2014. 66: 489.

12. Epstein, JI, *et al*: The 2014 International Society of Urological Pathology (ISUP)

Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol, 2016. 40:244.

13. Hayes, J.H., *et al.* Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. JAMA, 2014. 311: 1143.51

14. Schröder, F.H., *et al.* Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet, 2014. 384: 2027.

15. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet, 2012. 380: 1778.

16. Banerji, J.S., *et al.* Prostate Needle Biopsy Outcomes in the Era of the U.S. Preventive Services Task Force Recommendation against Prostate Specific Antigen Based Screening. J Urol, 2016. 195: 66.

17. Arnsrud Godtman, R., *et al.* Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Goteborg randomized population-based prostate cancer screening trial. Eur Urol, 2015. 68: 354.

18. Vickers, A.J., *et al.* Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. BMJ, 2013. 346: f2023.

19. Carlsson, S., *et al.* Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. BMJ, 2014. 348: g2296.

20. Louie, K.S., *et al.* Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. Ann Oncol, 2015. 26:848.

21. Droz, J.P., *et al.* Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. Lancet Oncol, 2014. 15: e404.

22. Eggener, S.E., *et al.* Empiric antibiotics for an elevated prostate-specific antigen (PSA) level: a randomised, prospective, controlled multi-institutional trial. BJU Int, 2013. 112: 925.

23. Loeb, S., *et al.* The Prostate Health Index: a new test for the detection of prostate cancer. Ther Adv Urol, 2014. 6: 74.

24. Bryant, R.J., *et al.* Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. J Natl Cancer Inst, 2015. 11: 107.

25. Hara, R., *et al.* Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. Urology, 2008. 71: 191.

26. Takenaka, A., *et al.* A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer Prostatic Dis, 2008. 11: 134.

27. Loeb, S., *et al.* Systematic review of complications of prostate biopsy. Eur Urol, 2013. 64: 876.

28. Futterer, J.J., *et al.* Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. Eur Urol, 2015. 68: 1045.

29. Le, J.D., *et al.* Magnetic resonance imaging-ultrasound fusion biopsy for prediction of final prostate pathology. J Urol, 2014. 192: 1367.

30. Moore, C.M., *et al.* Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol, 2013. 63: 125.

31. Siddiqui, M.M., *et al.* Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA, 2015. 313: 390.

32. Schoots, I.G., *et al.* Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol, 2015. 68: 438.

33. Panebianco, V., *et al.* Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol Oncol, 2015. 33: 17 e1.

34. Baco, E., *et al.* A Randomized Controlled Trial To Assess and Compare the Outcomes of Two-core Prostate Biopsy Guided by Fused Magnetic Resonance and Transrectal Ultrasound Images and Traditional 12-core Systematic Biopsy. Eur Urol, 2016. 69: 149.

35. Vache, T., *et al.* Characterization of prostate lesions as benign or malignant at multiparametric MR imaging: comparison of three scoring systems in patients treated with radical prostatectomy. Radiology, 2014. 272: 446.

36. Barentsz, J.O., *et al.* Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. Eur Urol, 2016. 69:41.

37. Albertsen, P.C. Observational studies and the natural history of screen-detected prostate cancer. Curr Opin Urol, 2015. 25: 232.

38. Wilt, T.J., et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med, 2012. 367: 203.

39. Albertsen P.C., *et al.* Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol, 2011. 29: 1335.

40. Thomsen, F.B., *et al.* Active surveillance for clinically localized prostate cancer--a systematic review. J Surg Oncol, 2014. 109: 830.

41. Loeb, S., *et al.* Active surveillance for prostate cancer: a systematic review of clinicopathologic variables and biomarkers for risk stratification. Eur Urol, 2015. 67: 619.

42. Montironi, R., *et al.* Consensus statement with recommendations on active surveillance inclusion criteria and definition of progression in men with localized prostate cancer: the critical role of the pathologist. Virchows Arch, 2014. 465: 623.

43. Schoots, I.G., *et al.* Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. Eur Urol, 2015. 67: 627.

44. Klotz, L., et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol, 2010. 28: 126.

45. Steuber, T., *et al.* Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. J Urol, 2006. 175: 939.

46. de Rooij, M., *et al.* Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. Eur Urol, 2016. 70:233.

47. Vickers, A.J., *et al.* The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. Lancet Oncol, 2009. 10: 475.

48. Ramsay, C., *et al.* Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technol Assess, 2012. 16: 1.

49. Briganti, A., *et al.* Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. Eur Urol, 2012. 61: 480.

50. Briganti, A., *et al*. Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. Eur Urol, 2006. 50: 1006.

51. Messing, E.M., *et al*. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol, 2006. 7: 472.

52. Abdollah, F., *et al*. Impact of Adjuvant Radiotherapy on Survival of Patients With Node-Positive Prostate Cancer. J Clin Oncol, 2014. 32: 3939.

53. Bill-Axelson, A., *et al*. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med, 2014. 370: 932.

54. Schreiber D., *et al*. Prostate biopsy concordance in a large population-based sample: a Surveillance, Epidemiology and End Results study. J Clin Pathol. 2015. 68: 453.

55. Yossepowitch, O., *et al*. Secondary therapy, metastatic progression, and cancer-specific mortality in men with clinically high-risk prostate cancer treated with radical prostatectomy. Eur Urol, 2008. 53: 950.

56. Walz, J., *et al*. Pathological results and rates of treatment failure in high-risk prostate cancer patients after radical prostatectomy. BJU Int, 2011. 107: 765.

57. Spahn, M., *et al*. Outcome predictors of radical prostatectomy in patients with prostate-specific antigen greater than 20 ng/ml: a European multi-institutional study of 712 patients. Eur Urol, 2010. 58: 1.

58. Joniau S, *et al*. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study. Eur Urol. 2015. 67:157.

59. Ficarra, V., *et al*. Systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol, 2012. 62: 405.

60. Haglind, E., *et al*. Urinary Incontinence and Erectile Dysfunction After Robotic Versus Open Radical Prostatectomy: A Prospective, Controlled, Nonrandomised Trial. Eur Urol, 2015. 68: 216.

61. Zelefsky, M.J., *et al.* Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys, 2008. 70: 1124.

62. Kuban, D.A., *et al.* Long-term failure patterns and survival in a randomized dose-escalation trial for prostate cancer. Who dies of disease? Int J Radiat Oncol Biol Phys, 2011. 79: 1310.

63. Zietman, A.L., *et al.* Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/American College of Radiology 95-09. J Clin Oncol, 2010. 28: 1106.

64. Beckendorf, V., *et al.* 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys, 2011. 80: 1056.

65. Heemsbergen, W.D., *et al.* Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol, 2014. 110: 104.

66. Kalbasi, A., *et al.* Dose-Escalated Irradiation and Overall Survival in Men With Non-metastatic Prostate Cancer. JAMA Oncol, 2015. 1: 897.

67. Koontz, B.F., *et al.* A systematic review of hypofractionation for primary management of prostate cancer. Eur Urol, 2015. 68: 683.

68. Jones, C.U., *et al.* Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med, 2011. 365: 107

69. Bolla, M., *et al.* External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol, 2010. 11: 1066.

70. Bolla, M., *et al.* Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med, 2009. 360: 2516.

71. Pilepich, M.V., *et al.* Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma--long-term results of phase III RTOG 85-31. Int J Radiat Oncol Biol Phys, 2005. 61: 1285.

72. Mason, M.D., *et al.* Final Report of the Intergroup Randomized Study of Combined Androgen- Deprivation Therapy Plus Radiotherapy Versus Androgen-Deprivation Therapy Alone in Locally Advanced Prostate Cancer. J Clin Oncol, 2015. 33: 2143.

73. Fizazi K., *et al*. Androgen deprivation therapy plus docetaxel andestramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial Lancet Oncol 2015. 16: 787.

74. Lawton, C.A., *et al.* An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys, 2007. 69: 646.

75. James N., *et al*. Failure-free survival and radiotherapy in patients with newly diagnosed nonmetastatic prostate cancer: Data from patients in the control arm of the STAMPEDE trial. .JAMA Oncol 2016. 2:348.

76. Bolla, M., *et al.* Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet, 2012. 380: 2018.

77. Wiegel, T., *et al.* Adjuvant Radiotherapy Versus Wait-and-See After Radical Prostatectomy: 10-year Follow-up of the ARO 96-02/AUO AP 09/95 Trial. Eur Urol, 2014. 66: 243.

78. Thompson, I.M., *et al.* Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol, 2009. 181: 956.

79. Fossati N, *et al*. Assessing the Optimal Timing for Early Salvage Radiation Therapy in Patients with Prostate-specific Antigen Rise After Radical Prostatectomy. Eur Urol, 2016. 69: 728.

80. Wallis, CJ, *et al.* Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. BMJ, 2016. 352: i851.

81. Ash, D., *et al.* ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. Radiother Oncol, 2000. 57: 315.

82. Grimm, P., *et al.* Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. BJU Int, 2012. 109 Suppl 1: 22.

83. Budäus, L., *et al.* Functional outcomes and complications following radiation therapy for prostate cancer: a critical analysis of the literature. Eur Urol, 2012. 61: 112.

84. Vordermark, D., *et al.* 3-D conformal treatment of prostate cancer to 74 Gy vs. high-dose-rate brachytherapy boost: a cross-sectional quality-of-life survey. Acta Oncol, 2006. 45: 708.

85. Hoskin, P.J., *et al.* GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: an update. Radiother Oncol, 2013. 107: 325.

86. Ramsay, C.R., *et al.* Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess, 2015. 19: 1.