EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

Prostate Cancer

P. Cornford (Chair), D. Tilki (Vice-chair), R.C.N. van den Bergh, D. Eberli, V. Fonteyne, G. Gandaglia, S. Gillessen, A.M. Henry, G.J.L.H. van Leenders, J. Oldenburg, I. van Oort, D.E. Oprea-Lager, M. Roberts, O. Rouvière, M. De Santis, I.G. Schoots, J. Stranne, T. Wiegel
Patient Advocates: E. Briers, B. Matsen
Guidelines Associates: P. Chiu, A. Epure, A. Farolfi, N. Grivas, E. Linares Espinós, A. Sachdeva
Guidelines Office: E.J. Smith

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1. INTRODUCTION

1.1 Aims and scope

The Prostate Cancer (PCa) Guidelines Panel have prepared this guidelines document to assist medical professionals in the evidence-based management of PCa.

It must be emphasised that clinical guidelines present the best evidence available to the experts, but following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients but rather help to focus decisions, also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The PCa Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, radiologists, pathologists and patient representatives.

All imaging sections in the text have been developed jointly with the European Society of Urogenital Radiology (ESUR) and the European Association of Nuclear Medicine (EANM). Representatives of the ESUR are Prof. Dr. O. Rouvière and Dr. I.G. Schoots and the EANM are Dr. A. Farolfi and Dr. D. Oprea-Lager. All radiotherapy (RT) sections have been developed jointly with the European Society for Radiotherapy & Oncology (ESTRO). Representatives of ESTRO are Prof.Dr. A.M. Henry, Prof.Dr. T. Wiegel and Prof.Dr. V. Fonteyne. The International Society of Urological Pathology (ISUP) is represented by Prof.Dr. A. van Leenders. The patient organisation Europa Uomo is represented by Erik Briers and Bo Matsen.

All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: https://uroweb.org/guideline/prostate-cancer/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available online and in print. This is an abridged version, which may require consultation together with the full text version. Numerous scientific publications are available, all of which can be accessed on the EAU website: https://uroweb.org/guideline/prostate-cancer/. An EAU Guidelines App for iOS and Android devices is also available containing the Pocket Guidelines, interactive algorithms and calculators, clinical decision support tools, guidelines cheat sheets and links to the extended guidelines.

1.4 Publication history and summary of changes

*1.4.1 **Publication history***

The EAU PCa Guidelines were first published in 2001. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. This 2026 PCa Guidelines present a limited update of the 2025 publication.

*1.4.2 **Summary of changes***

For the 2026 PCa Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature for all sections of the Guidelines. Key changes include:

- Review and changes to summary of evidence and recommendation in:
  - Section 5.5.7: Recommendations for MRI imaging in biopsy indication and strategy.
  - Section 5.8.5: Recommendations for staging of prostate cancer.
  - Section 6.2.1.c: Summary of evidence and recommendations for active surveillance strategy.
  - Section 6.4.4.d: Recommendations for imaging in patients with biochemical recurrence.
  - Section 6.4.7: Recommendations for second-line therapy after treatment with curative intent.
  - Section 6.6.8: Recommendations for the first-line treatment of hormone-sensitive metastatic disease.
  - Section 6.7.13: Recommendations for systemic treatments of castrate-resistant disease.
- Review and adaption of Table 4.3: EAU risk groups for localised and locally advanced PCa.
- Addition of a new table:
  - Table 5.4: Available risk calculators assessing the risk of csPCa (externally validated five or more times).
- Review and adaption of figures:
  - Figure 5.1: Flow diagram to assist with decisions on prostate biopsy.
  - Figure 6.5: Treatment of metastasized (M1*) - disease, M+HSPC.

- Significant review and adaption of sections:
  - Section 5.2.4: Magnetic resonance imaging.
  - Section 5.8.2.f.1: Pelvic lymph node dissection.
  - Section 6.4.5.a.3: Salvage lymph node dissection.
- Addition of new sections:
  - Section 5.3.2.g: Rare aggressive PCa (sub)types.
  - Section 5.4.3: Micro-US-based indication for biopsy.
  - Section 5.5.6: MRI-targeted biopsy in younger men (45-55 years).
  - Section 6.7.9: Treatment emergent neuroendocrine PCa and neuroendocrine subtype.
- Addition of new subsections in Section 6.6.4.b.2: Androgen deprivation therapy combined with chemotherapy:
  - Triplet therapy: ADT and chemotherapy +/- ARPI.
  - ADT and ARPI +/- PARPI (AMPLITUDE).
  - ADT and ARPI +/- AKT inhibitor (CAPItello-281).

2. METHODS

2.1 Data identification

For the 2026 Prostate Cancer (PCa) Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. Several comprehensive searches were performed, covering all sections of the PCa Guidelines. The searches were limited to English-language publications. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between 1 May 2024 and 1 May 2025. A total of 3,060 unique records were identified, retrieved and screened for relevance. Detailed search strategies are available online: https://uroweb.org/guideline/prostate-cancer/?type=appendices-publications.

Changes in recommendations were generally only considered based on high-level evidence (i.e. systematic reviews [SRs] with meta-analysis, randomised controlled trials [RCTs] and prospective comparative studies).

Recommendations within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates) and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [1];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2].

Additional methodology information and a list of associations endorsing the EAU Guidelines is available online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

The 2026 PCa Guidelines will be peer reviewed following publication. All reviewer comments and discussions points will be incorporated into the 2027 edition of the guidelines.

2.3 Future goals

Results of ongoing projects will be included in the 2027 update of the PCa Guidelines:

- Care pathways for the various stages of PCa management have been developed. These pathways will, in time, inform treatment flowcharts and a new EAU clinical decision support tool for PCa.

3. EPIDEMIOLOGY AND AETIOLOGY

3.1 Epidemiology

Prostate cancer is the second-most diagnosed cancer in men, with an estimated 1.46 million diagnoses and 396,792 deaths worldwide in 2022 [3, 4]. In more than half of the countries of the world, PCa is the most frequently diagnosed cancer in men and is the leading cause of death among men in a quarter of all countries [5]. In Europe, PCa is the most frequently diagnosed cancer in men and the third most common cancer-related cause of death in men [6].

An SR of autopsy studies reported a prevalence of PCa at age < 30 years of 5% (95% confidence interval [CI]: 3-8%), increasing with age to a prevalence of 59% (48-71%) by age > 79 years [7]. There is variation in the frequency of autopsy-detected PCa among men with different ethnical backgrounds and geographical areas (e.g. 83% in White US males vs. 41% in Japan at age 71-80) [8].

Regarding incidence of PCa diagnosis, the variation is even more pronounced among geographical areas, partly driven by rate of prostate-specific antigen (PSA) testing and influenced by the recommendation of national/international organisations on screening (see Section 5.1) [9]. PCa diagnosis is highest in Australia/New Zealand and Northern America (age-standardised rates [ASR] per 100,000 of 111.6 and 97.2, respectively), and in Western and Northern Europe (ASRs of 94.9 and 85, respectively) [10]. Incidence is low in Eastern and South-Central Asia (ASRs of 10.5 and 4.5, respectively) but is rising [11]. Rates in Eastern and Southern Europe were low but have also shown a steady increase [8, 12]. Other reasons for variation in PCa incidence include the age of the population, ethnicity and dietary factors [5].

There is relatively less variation in mortality rates worldwide, although rates are generally high in populations of African descent (e.g. Caribbean: ASR of 29, and Sub-Saharan Africa: ASRs ranging between 14 and 19), intermediate in the USA, and very low in Asia (South-Central Asia: ASR of 2.9) [5, 12]. Mortality due to PCa has decreased in most Western nations but the magnitude of the reduction varies between countries [3].

3.2 Aetiology and risk factors for prostate cancer

A wide variety of endogenous and exogenous/environmental factors have been discussed as being associated with the risk of developing PCa, or as being aetiologically important for the progression from latent to clinical PCa [13]. As discussed previously, there is likely a racial factor involved, but first-generation Asian immigrants in the USA have approximately half the risk of PCa when compared to their US-born Asian-descendant compatriots, implying a role for environmental and/or dietary factors [14]. These guidelines divide the risk factors into hereditary - such as ethnicity, family history and known genetic mutations - in which direct heritance of the risk factor is more obvious and direct, and nonhereditary - such as dietary and medical factors, as well as metabolic syndrome and obesity - in which hereditary components may well be involved, but they are more indirect.

3.2.1 Hereditary risk factors for PCa

There are three basic inherited risk factors that are consistently associated with PCa: ethnicity/family history, rare germline mutations in various candidate genes and common genetic single-nucleotide polymorphism (SNPs).

3.2.1.a Ethnicity and Family history

Ethnic background and family history are both associated with varying PCa incidence, suggesting a genetic predisposition [5]. Men of African ancestry in the Western world demonstrate more unfavourable outcomes, that may be due to biological, environmental, social and/or health-care factors [15]. These men have been reported to be at increased risk of being diagnosed with more advanced disease [16] and more likely to be upgraded after prostatectomy than White men [17], but the question is more intricate than that. In a population, race is categorised based on a combination of factors including ancestry, skin colour and geographical origin, and within any race there are hundreds of areas of geographical origins [5]. Indeed, a multiancestry polygenic risk score of 278 risk variants showed a strong association with PCa risk in men with African ancestry, particularly

sub-Saharan, and could potentially be used to identify susceptibility in this high-risk population [18]. There is also data suggesting no difference in overall survival (OS) or prostate cancer-specific mortality (PCSM) between White, Black or Hispanic men with metastatic PCa [19]. Racial disparities in accessing both screening and therapies for PCa may exist. It should be noted that very few PCa treatment trials report on race, education and socioeconomics [20]. Moreover, participation in a clinical trial is preceded by a selection process and most PCa studies include either small percentages of non-White men, or focus on other, highly specific groups which might affect the applicability of treatments [21, 22]. A systematic review also found that Black men without PCa appear to have higher baseline levels of PSA, which could lead to increased detection and further affect described differences [23].

A small subpopulation of all men with PCa, regardless of ethnicity, have true hereditary PCa (HPCa), defined as ≥ 3 cases in the same family, PCa in three successive generations or ≥ 2 cases in the same family diagnosed < 55 years. In a Swedish population-based study, the probability of high-risk PCa at age 65 was 11.4% (vs. a population risk of 1.4%), and for any PCa 43.9% (vs. 4.8%) if the father as well as two brothers were affected [24]. In a large USA population database, HPCa was also reported by 2.18% of participants, and showed a relative risk (RR) of 2.30 for diagnosis of any PCa, 3.93 for early-onset PCa, 2.21 for lethal PCa, and 2.32 for clinically significant PCa (csPCa) [25].

Familial PCa is defined as ≥ 2 first- or second-degree relatives with PCa on the same side of the pedigree. In this group and in those with known familial syndromes such as hereditary breast and ovarian cancer and Lynch syndrome, data from the UK suggests higher awareness of the risks and adherence to screening might decrease PCSM [26]. In both groups the more members affected the higher the risk [24].

Table 3.1: Definition of familial and hereditary PCa

Type	Definition
Familial	2 first-degree relatives diagnosed with PCa at any age or 1 first-degree relative and ≥ 2 second-degree relatives diagnosed at any age.
Hereditary	≥ 3 cases in the same family, PCa in three successive generations, or ≥ 2 cases in the same family diagnosed < 55 yrs.

3.2.1.b Germline mutations

Pathogenic germline mutations in the *BRCA2* and *HOXB13* genes, but also in the genes *CHEK2*, *BRCA1*, *ATM*, *NBS1*, and genes involved in Lynch syndrome, have been suggested to increase the risk of PCa [5]. Data from the United Kingdom on over 21,000 men without a PCa diagnosis suggest that 1.6% carry a pathogenic mutation in at least one of the genes *BRCA2*, *HOXB13* or *CHEK2*. Although germline mutations leading to PCa are relatively rare (1/300), the impact on PCa risk is quite strong, and the prevalence in patients with advanced PCa is high [27]. In a study of 3,607 unselected patients with PCa diagnosis, as many as 17.2% had a pathogenic mutation [28]. In men with PCa undergoing multigene testing across the United States, 15.6% of men with PCa were found to have pathogenic variants identified in genes tested (*BRCA1, BRCA2, HOXB13, MLH1, MSH2, PMS2, MSH6, EPCAM, ATM, CHEK2, NBN,* and *TP53*), and 10.9% of men were found to have germline pathogenic variants in DNA repair genes (Table 3.2) [29]. Pathogenic variants were most commonly identified in *BRCA2* (4.5%), *CHEK2* (2.2%), *ATM* (1.8%) and *BRCA1* (1.1%) [29].

Among men with metastatic PCa, an incidence of 11.8% was found for germline mutations in genes mediating DNA-repair processes [30], and for patients diagnosed with metastatic castrate-resistant PCa (mCRPC), the incidence was 16.2% [31]. Targeted genomic analysis of genes associated with an increased risk of PCa could offer options to identify families at high risk [32, 33].

A prospective cohort study of male *BRCA1* and *BRCA2* carriers confirmed *BRCA2* association with aggressive PCa [34]. An analysis of the outcomes of 2,019 patients with PCa (18 *BRCA1* carriers, 61 *BRCA2* carriers and 1,940 noncarriers) showed that PCa with germline *BRCA1/2* mutations were more frequently associated with ISUP grade group (GG) ≥ 4, stage T3/T4, nodal involvement and metastases at diagnosis than PCa in noncarriers [35]. *BRCA*-susceptibility gene mutation carriers were also reported to have worse outcome when compared to noncarriers after local therapy [36]. In a retrospective study of 313 patients who died of PCa and 486 patients with low-risk localised PCa, the combined *BRCA1/2* and *ATM* mutation carrier rate was significantly higher in lethal PCa patients (6.1%) than in localised PCa patients (1.4%) [37].

Table 3.2: Germline mutations in DNA repair genes associated with increased risk of PCa

Gene	Location	PCa risk	Findings
BRCA2	13q12.3	RR 2.5 to 4.6 [38, 39] PCa at 55 years or under: RR: 8-23 [40, 41]	Up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA2* [5.3%]) [30]
			2% of men with early-onset PCa harbour germline mutations in the *BRCA2* gene [40]
			BRCA2 germline alteration is an independent predictor of metastases and worse PCa-specific survival [35, 42]
HOXB13	17q21.2	OR 3.4-7.9 [32, 43]	Significantly higher PSA at diagnosis, higher Gleason score and higher incidence of positive surgical margins in the RP specimen than noncarriers [44]
CHEK2	22q12.1	OR 3.3 [38, 39]	Up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *CHEK2* [1.9%]) [30]
BRCA1	17q21	RR: 1.8-3.8 at 65 years or under [45, 46]	Higher rates of lethal PCa among mutation carriers [37]
			Up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *BRCA1* [0.9%]) [30]
ATM	11q22.3	RR: 6.3 for metastatic PCa [30]	Higher rates of lethal PCa among mutation carriers [37]
			Up to 12% of men with metastatic PCa harbour germline mutations in 16 genes (including *ATM* [1.6%]) [30]
MMR genes *MLH1* *MSH2* *MSH6* *PMS2*	 3p21.3 2p21 2p16 7p22.2	RR: 3.7 [47]	Mutations in MMR genes are responsible for Lynch syndrome [48] *MSH2* mutation carriers are more likely to develop PCa than other MMR gene mutation carriers [49]

ATM = ataxia telangiectasia mutated; BRCA1 = breast cancer gene 1; BRCA2 = breast cancer gene 2; CHEK2 = checkpoint kinase 2; GS = Gleason score; HOXB13 = homeobox B13; MLH1 = mutL homolog 1; MMR = mismatch repair; MSH2 = mutS homolog 2; MSH6 = mutS homolog 6; OR = odds ratio; PCa = prostate cancer; PMS2 = post-meiotic segregation increased 2; PSA = prostate-specific antigen; RP = radical prostatectomy; RR = relative risk.

3.2.1.c Genetic single nucleotide polymorphism (SNPs)

If germline genetic mutations are relatively rare, but with significant impact on PCa risk, SNPs are very common, but each SNP has low impact on the risk of developing PCa [5]. Two hundred and sixty-nine individual SNPs have been identified to be associated with PCa risk [50]. Although each individual SNP has a low impact on PCa risk, the additive effects of multiple alleles can cause substantial increased risk of developing PCa and are likely causative of a large proportion of hereditary PCa [51]. The additive effect of the different SNPs can be summed into polygenic risk scores (PRSs), which are directly associated with the absolute risk of developing PCa [18, 52]. Thus far, however, there appears to be no additive prognostic value in the PRSs when added to PSA and PRSs therefore cannot be used for risk stratification [51].

3.2.2 Non-hereditary risk factors for PCa

There are a number of risk factors for PCa, which are less determined by ethnicity and/or heredity, of which age is the most obvious [7].

3.2.2.a Metabolic syndrome

The association between metabolic syndrome and PCa is not clear, with mixed results in various studies. There appears to be a weak association overall, but a slightly stronger association in the subgroup of men with more aggressive disease [5]. The single components of metabolic syndrome that have been the most strongly associated with a significantly greater risk of PCa are hypertension ($p = 0.035$) and waist circumference ≥ 102 cm ($p = 0.007$) [53]. A SR found a slightly reduced risk of PCa, from anti-hypertension medication with renin-angiotensin inhibitors, while the use of calcium channel blockers was suggested to be associated with a slightly higher risk [54].

3.2.2.a.1 *Obesity*

Within the REDUCE study, obesity was associated with lower risk of low-grade PCa (OR: 0.79, p = 0.01) and a higher risk of high-grade PCa (OR: 1.28, p = 0.042) in multivariable analyses [55]. This effect appears mainly to be explained by environmental determinants of height/body mass index (BMI) rather than genetically elevated height or BMI [56]. An SR showed an association between obesity and increased PC-specific incidence and mortality [57, 58].

3.2.2.a.2 *Diabetes/metformin*

An SR from 2021 could not identify any association between diabetes type 2 and PCa [59]. However, another SR including 43 studies and over 3.7 million patients, concluded that diabetes (type not specified) was associated with a reduced risk of PCa [60]. The association between metformin use and PCa is controversial. At population level, metformin users (but not other oral hypoglycaemic agents) were found to be at a decreased risk of PCa diagnosis compared with never users (adjusted OR: 0.84; 95% CI: 0.74-0.96) [61], a result that was replicated in a meta-analysis (RR: 0.82, 95% CI: 0.74-0.91) [62]. In 540 diabetic participants of the REDUCE study, metformin use was not significantly associated with PCa and therefore not advised as a preventive measure (OR: 1.19, p = 0.50). Moreover, the STAMPEDE trial randomised 1,874 patients with high-risk locally advanced or metastatic PCa to standard of care +/- metformin and did not find any survival benefit from addition of metformin (HR 0·91, 95% CI 0·80-1·03; p=0·15) [63, 64].

3.2.2.a.3 *Cholesterol/statins*

A meta-analysis of fourteen large prospective studies did not show any association between blood total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol levels, and the risk of developing either overall PCa or high-grade PCa [51]. Two meta-analyses suggested a lower risk of PCa overall (OR: 0.94), as well as advanced PCa in statin users [65, 66]. Pooled estimates indicated that the effect seemed to be exclusive to lipophilic statins [65].

3.2.2.b Dietary factors

The association between a wide variety of dietary factors and PCa have been studied, but there is a paucity of quality evidence (Table 3.3). To date, the current body of evidence will not support a causal relationship between specific (dietary and otherwise) factors and the development of PCa. Consequently, no effective preventative strategies can be suggested.

Table 3.3: Main dietary factors that have been associated with PCa

Alcohol	High alcohol intake, but also total abstention from alcohol has been associated with a higher risk of PCa and PCa-specific mortality [67]. A meta-analysis suggests a weak relationship with PCa [68].
Coffee/Tea	Coffee consumption may be associated with a reduced risk of PCa, with a pooled RR of 0.91 for the highest category of coffee consumption [69]. No clear association was found between tea consumption and PCa risk [5].
Dairy/Calcium	An SR suggests a correlation between high intake of protein from dairy products and the risk of PCa was found, but many of the included studies were affected by PSA screening bias [70, 71].
Fat	No association between intake of long-chain omega-3 poly-unsaturated fatty acids and PCa was found [72]. A relation between intake of fried foods and risk of PCa may exist [73].
Ultra-Processed food	A systematic review suggests no significant association between ultra-processed foods, known for their high content of additives and preservatives and low levels of whole-food ingredients, and PCa [74].
Tomatoes (lycopenes/ carotenes)	A trend towards a favourable effect of tomato intake (mainly cooked) and lycopenes on PCa incidence has been identified in meta-analyses [75, 76]. Randomised controlled trials (RCTs) comparing lycopene with placebo did not identify a significant decrease in the incidence of PCa [77].
Plant-based diets	An SR on the association between plant-based diets and PCa suggest a small beneficial impact on PCa risk [78]. Another SR/meta-analyses, including a total of 16 studies and > 1.2 million men, suggested a linear association between higher intake of cruciferous vegetables and a lower risk of PCa [79].

Meat	Meta-analyses show a potential association between red meat, total meat, and processed meat consumption and PCa [80, 81].
Fish	An SR/meta-analysis comparing men with high versus low intake of fish over time could not find an association between fish intake and risk of PCa. However, there was a strong association with high intake of fish and PCSM (RR 0.55), as well as PCa progression (RR 0.84) [82].
Soy (phytoestrogens [isoflavones/ coumestans])	Phytoestrogen intake was significantly associated with a reduced risk of PCa in a meta-analysis [66]. Total soy food intake has been associated with a reduced risk of PCa [83, 84].
Vitamin D	A U-shaped association has been observed, with both high and low vitamin-D concentrations, being associated with an increased risk of PCa, and a stronger association with high-grade disease [75, 76].
Vitamin E/Selenium	An inverse association between selenium blood, but mainly nail, levels (reflecting long-term exposure) with aggressive PCa has been found [85, 86]. Selenium and Vitamin E supplementation; however, were found not to affect PCa incidence [87].

3.2.2.c Hormonally active medication

3.2.2.c.1 5-alpha-reductase inhibitors (5-ARIs)

Although it appears that 5-ARIs have the potential of preventing or delaying the development of PCa (decreasing the risk by 25% but only for ISUP GG 1 cancer), this must be weighed against treatment-related side effects as well as the potential small increased risk of high-grade PCas (although this does not appear to impact PCa mortality) [88-90]. None of the available 5-ARIs have been approved by the European Medicines Agency (EMA) for chemoprevention.

3.2.2.c.2 Testosterone

Hypogonadal men receiving testosterone supplements do not have an increased risk of developing PCa [91]. A pooled analysis showed that men with very low concentrations of free testosterone (lowest 10%) have a below average risk (OR: 0.77) of PCa [92]. Furthermore, although the evidence is limited, men who are managed expectantly for PCa, or who received radical curative therapy, do not have worse outcomes when receiving testosterone supplementation, despite a theoretical higher risk of progression after correction of the hypogonadal situation [93].

3.2.2.d Other potential risk factors

Taller height, potentially due to higher levels of insulin-like growth factor during puberty, and vertex pattern baldness, has been reported to be associated with an increased risk of PCa [5, 94].

A significantly higher rate of ISUP GG ≥ 2 PCa (hazard ratio [HR]: 4.04) was found in men with inflammatory bowel disease (IBD) when compared with the general population [95]. However, in an SR, the results on IBD overall were mixed, except for the subgroup of ulcerative colitis, where a clear association could be seen [5].

Increased occupational physical activity appears to be associated with reduce PCa risk while occupational exposure to chemicals and pesticides increases the risk [5]. Plasma concentration of the estrogenic insecticide chlordecone is associated with an increase in the risk of PCa (OR: 1.77 for highest tertile of values above the limit of detection) [96]. Meta-analyses indicate that night-shift work is associated with an increased risk of PCa in a dose-dependent manner [5, 97]. There have been reports of an increased risk among firefighters and police officers, but the studies had high heterogeneity, and the results may be hampered by a high rate of PSA testing among the included men. A meta-analysis on Cadmium (Cd) found a positive association between high Cd exposure and risk of PCa (OR 1.11, 95% CI 0.85-1.45) and for the aggressive histopathological type of PCa (OR 1.50, 95% CI 1.08-2.07). In most of the included studies Cd exposure was occupational, but there was a high level of heterogeneity between the studies [98].

Current cigarette smoking was associated with an increased risk of PCa death (RR: 1.24, 95% CI: 1.18-1.31) and with aggressive tumour features and worse prognosis, even after quitting smoking [99, 100].

Men positive for human papillomavirus type 16 may be at increased risk [101], and gonorrhoea has been significantly associated with an increased incidence of PCa (OR: 1.31; 95% CI: 1.14-1.52) [102].

A two-sample Mendelian randomisation study indicated a causal relationship between twelve specific gut microbial taxa and PCa. While these findings may be difficult to use clinically, they may offer new targets for PCa screening and treatment [103].

The use of aspirin or nonsteroidal anti-inflammatory drugs seems to have a protective effect on the risk of PCa [5]. Ultraviolet radiation exposure also decreased the risk of PCa (HR: 0.91, 95% CI: 0.88-0.95) [104], and a review found a small but protective association of circumcision status with PCa [105]. Higher ejaculation frequency (≥ 21 times a month vs. 4 to 7 times) has been associated with a 20% lower risk of PCa [106]. A number of other factors previously linked to an increased risk of PCa have been disproved, including vasectomy [107] and self-reported acne [108].

*3.2.3 **Summary of evidence for epidemiology and aetiology***

Summary of evidence	LE
Prostate cancer is a major health concern in men, with incidence mainly dependent on age and extent of PSA testing.	3
Genetic factors are associated with risk of (aggressive) PCa.	3
A variety of dietary/exogenous/environmental factors have been associated with PCa incidence and prognosis.	3
In hypogonadal men, testosterone supplements do not increase the risk of PCa.	2a
No conclusive data exist which could support specific preventive or dietary measures aimed at reducing the risk of developing PCa.	1a

4. CLASSIFICATION AND STAGING SYSTEMS

4.1 Classification

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This enables the following:

- discussion regarding prognosis and treatment with patients;
- design of clinical trials on relatively homogeneous populations;
- comparison of diagnostic and treatment outcomes from different hospitals across the world;
- development of recommendations for the treatment of these patient populations.

Throughout these Guidelines, the following are used:

- the Union for International Cancer Control (UICC) 8th edition (2017);
- the Tumour, Node, Metastasis (TNM) classification for staging of PCa (Table 4.1) [109]; and
- the EAU risk group classification [110].

The EAU risk classification is based on the D'Amico risk classification grouping patients with a similar risk of biochemical recurrence (BCR) after radical prostatectomy (RP) or external beam radiotherapy (EBRT). Increasing granularity, such as in NCCN and Cambridge Prognostic Groups, improves model performance for predicting PCSM compared to the EAU risk classification [111, 112]. Although the optimal risk stratification system remains to be defined, separation of the EAU intermediate-risk group into favourable and unfavourable intermediate-risk based on PSA and ISUP GG is recommended. Changes in the diagnostic pathway, such as imaging (e.g. MRI, Prostate-Specific Membrane Antigen [PSMA] Positron Emission Tomography Computed Tomography [PET/CT] scan) and biopsy (e.g. increasing number of systematic biopsy cores, targeted biopsy) may cause stage and grade shift, altering the risk profile of any specific classification systems [113]. This stage and grade shift should be taken into account in disease management decisions.

Although the 2017 American Joint Committee on Cancer (AJCC) staging 8th edition specifically states that clinical staging should be based on digital rectal examination (DRE) only, the UICC does not make such an explicit statement. Since clinical stage, as assessed by DRE only, is included in the EAU risk group classification, cT stage should be based on DRE findings and not on imaging. Additional staging information based on imaging should be reported separately. A nonpalpable PCa with bilateral positive biopsies and extraprostatic extension (EPE) on MRI would therefore be categorised as cT1c with a separate report of MRI findings.

Table 4.1: Clinical Tumour Node Metastasis (TNM) classification of PCa [109]

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

[1] *Nodal metastasis no larger than 0.2cm 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 pathological tissue assessment and largely parallels the clinical TNM, except for clinical T1 and T2 substages. Pathological stages pT1a/b/c do not exist and histopathologically confirmed organ-confined PCas after RP are pathological stage pT2. The current UICC no longer recognises pT2 substages [109].

Of note, the EANM proposed a molecular imaging TNM (miTNM) classification, taking into account PSMA PET/CT findings [114]. The prognosis of the miT, miN and miM substages is likely to be better than their T, N and M counterparts due to the 'Will Rogers phenomenon' - the extent of this prognosis shift, as well as its practical interest and impact, remains to be assessed [115]. This reclassification is not endorsed by the UICC or the AJCC.

4.2 Gleason score and International Society of Urological Pathology 2019 grade

In the original Gleason grading system, five Gleason grades (ranging from 1 to 5) were distinguished based on histological tumour architecture, but in the 2005 and subsequent 2014 ISUP consensus meetings, Gleason grades 1 and 2 were eliminated [116, 117]. The 2005 ISUP-modified Gleason score (GS) of biopsy-detected PCa comprises the Gleason grade of the most extensive (primary) pattern, plus the second most common (secondary) pattern, if two are present. If only one pattern is present, this pattern must be doubled to yield the GS. For three grades, the biopsy GS comprises the most common grade plus the highest grade, irrespective of its extent. If cribriform growth and intraductal carcinoma (IDC) is present intermixed with invasive PCa, this should be incorporated into the GS based on its underlying architectural pattern [118]. In addition to reporting of the carcinoma features for each biopsy site, providing an overall (or global) GS based on all carcinoma-positive

biopsies is optional. The global GS takes into account the cumulative extent of each grade from all prostate biopsies. The ISUP endorsed grading system limits the number of PCa grades from 1 to 5 (Table 4.2) [117, 119].

Table 4.2: International Society of Urological Pathology 2014 grade group system

Gleason score	ISUP 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 (4+5 or 5+4 or 5+5)	5

4.3 Clinically significant prostate cancer

The descriptor 'clinically significant' is widely used to differentiate PCa that may cause morbidity or death in a specific patient from types of PCa that rarely do. This distinction is particularly important as insignificant PCa is common [7]. Unless this distinction is made, such cancers are at high risk of being overtreated, with the treatment itself risking harmful side effects to patients. The overtreatment of insignificant PCas has also been criticised as a major drawback of population-based screening and individual early detection [120]. Although pathological factors are often used to delineate insignificant PCa, the definition of significant versus insignificant is a balance between tumour and patient factors. High-risk PCa is significant in almost all men, except when life expectancy is limited. Low-risk PCa is insignificant in almost all men.

From a pathological perspective, in large studies of RP specimens with only ISUP GG 1 disease, EPE (0.3%) [121] and biochemical recurrence (3.5%) were rare, and seminal vesicle (SV) invasion or lymph node (LN) metastasis did not occur at all [122, 123]. International Society of Urological Pathology GG 1 disease at RP itself can therefore be considered clinically insignificant and does not need oncological follow-up. Whilst ISUP GG 1 bears the hallmarks of cancer histologically, ISUP GG 1 at RP itself does not behave in a clinically malignant fashion [124]. It is important to note that the studies showing absence of metastasis in ISUP GG 1 were all conducted on RP specimens. Men with biopsy ISUP GG 1 who undergo operations for their disease have a low risk of postoperative BCR, metastasis and disease-specific death, particularly in case of high tumour biopsy volume and PSA levels due to under sampling of a higher-grade component [125]. In a contemporary retrospective study of men with cT1-T2 cN0 ISUP GG 1 PCa at mpMRI-targeted biopsy, 72% had ISUP GG ≥ 2, 9% had ISUP GG ≥ 3, 25% had pT3a and 4% had pT3b at subsequent RP [126]. In a Danish population-based registry study including men with localised biopsy ISUP GG 1 PCa diagnosed after 2006, 15-year PCSM was 1-4% for those initially treated by RP or RT, 5.5% for those on AS, and 14% for those commenced on WW [127]. Finally, modifications in PCa grading have led to a grade shift during the past twenty years. For example, the introduction of the ISUP grading modification in 2005 led to 20% of pre-ISUP 2005 GS 6 tumours being upgraded to GS 7 or higher, which must be taken into account when interpreting older studies [128].

The current practice of MRI-targeted and perilesional biopsies has improved diagnostic accuracy [129], however, sampling error may still occur such that higher grade cancer could be missed. In particular, this should be considered in case of high PSA density, high pathological biopsy tumour volume, and a visible lesion at MRI, but only ISUP GG 1 at biopsy [130, 131]. Another complexity in defining insignificant cancer is that ISUP GG 1 may progress to higher grades over time, at a rate of approximately 1% per year [132] and becoming clinically significant at a later biopsy [133].

Therefore, although ISUP GG 1 itself can be described as clinically insignificant, it is important to take into account other tumour-related factors, such as PSA, stage, imaging prior to biopsy and adequate sampling core number [125]. When combined with low-risk clinical factors (Table 4.3), ISUP GG 1 represents low-risk PCa and recommended management options are active surveillance (AS) or watchful waiting (WW) (see Sections 6.2.1.a and 6.2.1.b).

Epidemiological and autopsy data suggest that many ISUP GG 1 but also ISUP GG 2 PCas would remain undetectable during a man's life [134] and therefore may be overtreated. There is insufficient data to relate modern histological grading, obtained often after MRI, to hard clinical endpoints but the assumption that if ISUP GG 1 is insignificant so everything else must be clinically significant is not supported. Interestingly, papers have commonly defined clinically significant cancer, using ISUP GG 2 and above but without a clear rationale [135,

136]. Some groups have suggested ISUP GG 3 and above, or provide more than one definition within a single study [137, 138]. Since there is a lack of consensus it is imperative that authors define and state in their own studies what they believe csPCa is and why, including exactly how the disease was diagnosed.

Table 4.3: EAU risk groups for localised and locally advanced PCa

Definition				
Low risk	**Intermediate risk**		**High risk**	
	Favourable	**Unfavourable**		
ISUP GG 1 and PSA < 10ng/mL and cT1-2*	ISUP GG 2 and PSA < 10ng/mL and cT1-2* **Or** ISUP GG 1 and PSA 10-20ng/ml and cT1-2*	ISUP GG 2 and PSA 10-20ng/mL and cT1-2* **Or** ISUP GG 3 and cT1-2*	ISUP GG 4/5* **Or** PSA > 20ng/mL	cT3-4* and/or cN+** any ISUP GG* any PSA
Localised				**Locally advanced**

ISUP = International Society of Urological Pathology; PSA = prostate-specific antigen; GG = Grade group.
** Based on digital rectal examination.*
*** Based on CT/bone scan.*

4.4 Prognostic relevance of stratification

Tumour, Node, Metastasis (TNM) staging is a schematic representation of anatomic tumour extent and pathological grade is reflective of intrinsic features of tumour aggressiveness. The EAU risk group classification combines clinical information on tumour extent, PSA, and pathology from biopsy (Table 4.3). A more precise stratification of the clinically heterogeneous subset of intermediate-risk group patients could provide a better framework for their management [139, 140]. The Cambridge Prognostic Groups five-tier model based on ISUP GG, PSA and cT stage were shown to have significantly better discriminative performance than the current three-tier EAU risk groups for PCSM [141]. This model separates both EAU intermediate- and high-risk groups in clinically relevant subgroups and has been validated in several cohorts [141-143].

The current EAU classification of low-, favourable- and unfavourable-intermediate risk is essentially similar to the Cambridge Prognostic Groups subgroups. More recently, risk stratifications incorporating the 17-gene Genomic Prostate Score (GPS) [144-146], invasive cribriform and/or intraductal carcinoma (CR/IDC) [147, 148], and mpMRI [149], findings have shown better performance in predicting post-treatment BCR than the (former) three-tier EAU, NCCN and CAPRA models. Although incorporation of routinely available CR/IDC status and modern imaging findings are likely able to improve current risk stratification, validation in different PCa populations is required.

4.5 Recommendations for classification and staging systems

Recommendations	**Strength rating**
Use the Tumour, Node, Metastasis (TNM) classification for PCa staging.	Strong
Clinical stage should be based on digital rectal examination only; additional staging information based on imaging or pathology should be reported separately.	Strong
Use the International Society of Urological Pathology (ISUP) 2019 system for grading PCa.	Strong

5. DIAGNOSTIC EVALUATION

5.1 Individual early detection and screening

The diagnostic pathway for PCa aims to achieve detection of significant PCa, while leaving insignificant PCa undetected, balancing diagnostic accuracy with the burden on an individual and healthcare resources. Patient-specific factors such as lower urinary tract symptoms (LUTS), family history, age and comorbidity should always be considered.

Men may enter the diagnostic pathway through various indications, including clinical symptoms, opportunistic early detection (individual) or screening (population-based). The prevalence of PCa and significant PCa varies depending on the indication, resulting in different yields of the subsequent diagnostic pathway.

*5.1.1 **Prostate-specific antigen (PSA)***

Regardless of which pathway a patient goes through to his PCa diagnosis, a PSA test will be part of it. For more information on PSA, its production, function and sources of error in PSA assessment, see Section 5.2.2.

*5.1.2 **Clinical symptoms***

Symptoms usually occur late in the natural history of PCa, and localised PCa is therefore usually asymptomatic. Local progression may cause symptoms such as LUTS, erectile dysfunction (ED), retention, local pain, haematospermia, or haematuria. Bone metastases may cause pain or spinal cord compression. Digital rectal examination (DRE) and PSA are usually part of the initial diagnostic workup in these cases, after which a further diagnostic algorithm may be initiated. Definitive diagnosis normally depends on histopathological verification in prostate biopsy cores. However, men with high suspicion of malignancy (e.g. malignant feeling prostate, PSA > 100ng/mL and a positive bone scan) might avoid a biopsy, especially if pre-existing comorbidities would exclude any treatment intensification in the hormone-sensitive or castration-resistant phase in addition to ADT or any future second-line treatments.

*5.1.3 **Individual early detection***

Early detection may be initiated on an individual level, with or without concurring LUTS. As increasing age is a major risk factor for PCa there is very little point in starting diagnostic evaluation too early. In men with no other risk factors, the risk of having a clinically significant PCa (csPCa) under the age of 50 years is low. Therefore, early testing with PSA can be recommended starting at the age of 50. For men with a family history of PCa and for men of African descent, the corresponding age for testing is 45 years (see Section 3.2.1.a), and for men carrying BRCA2 mutations, the corresponding age is 40 years [150, 151].

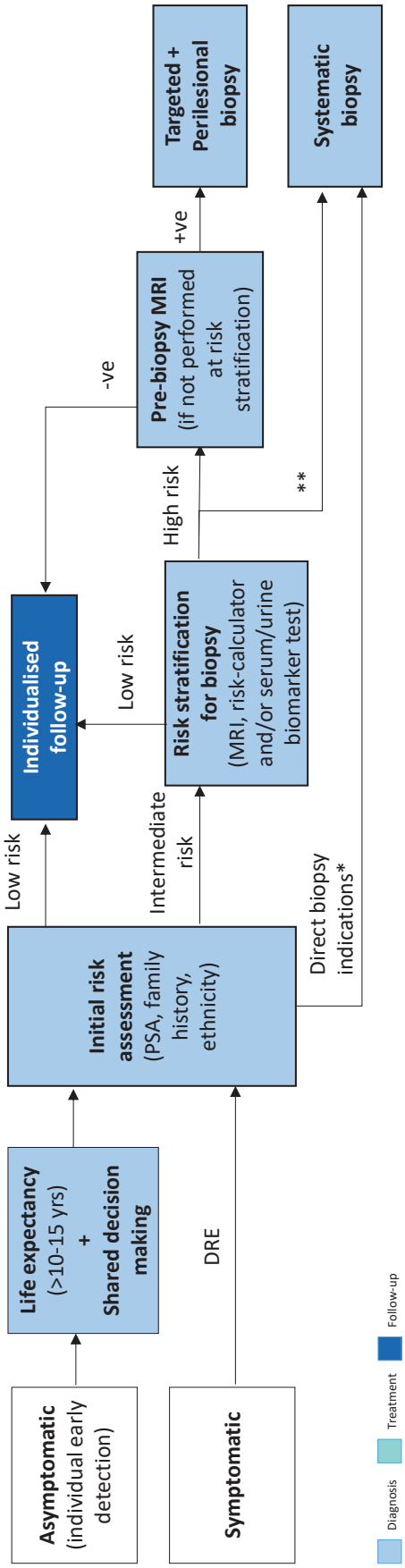
Individuals considering early detection should be aware of the lead time associated plus the risk of detecting clinically insignificant cancers, leading to possible overtreatment, as well as the possibility of improved disease-specific mortality. It is difficult to accurately estimate the individual benefit or harm due to early detection for the individual man, but the effect may be larger than in screening trials because diluting effects from intention-to-treat analyses in population-based intention-to-screen analyses are not applicable (i.e. non-participation: no participation after screening invitation; contamination: screening occurring in control arm) [152]. Nevertheless, a comparison of systematic and opportunistic screening suggested overdiagnosis and mortality reduction in the systematic screening group compared to a higher overdiagnosis with only a marginal survival benefit, at best, in the opportunistic screening regimen [153].

A baseline PSA may be used to predict PCa mortality after 12-20 years and can therefore be used to guide the frequency of follow-up. The risk of dying from PCa by age 85 is ≤ 0.2% for 60-year-old men with PSA concentration below the median of ≤ 1.0ng/mL [154]. Follow-up intervals of 8-10 years may be offered to a majority of men up to the age of 60, and 50% of the men may be reassured and exempted from further screening after the age of 60 years. Follow-up intervals of two years may be offered to those initially at risk (PSA > 1 ng/mL at 40 years; PSA > 2 ng/mL at 60 years) [155-157].

The age at which attempts at an early diagnosis should be stopped remains controversial, but an individual's life expectancy is the main driver and must be considered. Asymptomatic men who have less than a 15-year life expectancy are unlikely to benefit from an early diagnosis of prostate cancer, based on data from the Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the European Randomised Screening for Prostate Cancer (ERSPC) trials [158]. However, a substantial proportion of these men have prostate cancer that will not cause serious symptoms during their lifetime, meaning the risk of overdiagnosis is high. An even larger

proportion have elevated PSA levels due to benign prostatic hyperplasia (BPH), leading to investigations and follow-ups. Therefore, men with a life span of less than 10-15 years should not be PSA tested in the absence of symptoms or clinical signs of PCa. Nevertheless, there is no simple tool to evaluate individual life expectancy and comorbidity is at least as important as age. A detailed review can be found in Section 6.1 and the SIOG Guidelines [159]. Informed men with one of the risk factors above (including age), a life expectancy of > 15 years and requesting investigation should be given a PSA test and undergo a DRE, after which a further diagnostic algorithm may be initiated [160].

Figure 5.1: Flow diagram to assist with decisions on prostate biopsy



** PSA > 50, cT3-4*

*** If MRI not available/possible*

Population-based screening

Population screening is defined as the 'systematic examination of asymptomatic men to identify individuals at risk for a specific disease' and is usually initiated by health authorities. The co-primary objectives are:

- reduction in mortality due to PCa
- maintained quality of life (QoL) as expressed by QoL-adjusted gain in life years (QALYs)

Metastases free survival rates have also been considered as a relevant endpoint due to impact on QoL.

A Cochrane review of randomised PCa screening trials with PCa mortality as endpoint was published in 2013 [161] and updated in 2018 [162, 163]. The main findings of the updated publication from the results of five RCTs, randomising more than 721,718 men, are:

- Screening is associated with an increased diagnosis of PCa (Incidence ratio [IR]: 1.23, 95% CI: 1.03-1.48).
- Screening is associated with detection of more localised disease (RR: 1.39, [1.09-1.79]) and less advanced PCa (T3-4, N1, M1; RR: 0.85 [0.72-0.99]).
- No PCa-specific survival benefit was observed (IR: 0.96 [0.85-1.08]). This was the main endpoint in all trials.
- No overall survival (OS) benefit was observed (IR: 0.99, 95% CI: 0.98-1.01). None of the trials were designed/ powered for this endpoint.

The included studies differ in multiple aspects, including trial size, time periods, age groups, participation/ compliance rates, previous screening rates (opportunistic testing in control arm, 'contamination'), one-time screening (i.e., prevalence screening, where patients are invited for PSA test at one time only) vs. repeat screening (where patients are repeatedly invited for PSA-testing over time), and the applied diagnostic pathway. These heterogeneities account for discrepancies in results between single studies and aggregated findings of the Cochrane review and makes the results of the latter difficult to interpret.

Two studies showed a favourable impact of screening: ERSPC and CAP. The CAP study after 15-year follow-up, showed a small but significant reduction in PCSM, despite being only a one-time PSA screening [164].

The ERSPC study started in the early 90s, including > 182,000 European men, found a significant reduction in PCa mortality due to screening. ERSPC applied a mainly PSA-based screening protocol (cut-off 3.0-4.0ng/mL followed by systematic sextant prostate biopsy, every two to four years in men aged 50-74) [158]. The contamination rate was relatively low when compared to other large studies, such as the Prostate Lung Colorectal and Ovarian (PLCO) screening trial [165]. A limitation is the heterogeneity in patient groups and the applied screening protocols. Since 2013, data have been updated with twenty-three years of follow-up [158, 166]. With extended follow-up, the mortality reduction (21% and 29% after non-compliance adjustment) remains unchanged. However, the number needed to screen (NNS), the number needed to diagnose (NND) and the number needed to treat (NNT) is decreasing and is now below the NNS observed in breast cancer trials [158, 167] (Table 5.1).

Table 5.1: Follow-up data from the ERSPC study [158, 166]

Years of follow-up	Number needed to screen	Number needed to treat
9	1,410	48
11	979	35
13	781	27
16	570	18
23	456	12

In the Rotterdam section of the ERSPC with 21 years of follow-up, the risk ratio of death due to PCa was 0.73 in the screening group, with NNS of 246 and NND of 14 to prevent one death due to PCa [168]. To prevent one metastasized case NNS was 121 and NND seven.

In the Goteborg screening trial, with 18 years of follow-up, the ratio of death from PCa for the screening group compared with the control group was 0.65 (95% CI: 0.49-0.87), and for men commencing screening at age 55-59 it was 0.47 (95% CI: 0.29-0.78) [169]. The NNS was 231 and 10 for the NND. After 22 years of follow-up, the corresponding NNS was 221 and NND was nine, and the highest risk of PCSM was identified in men who started screening at the age of 60 years and in non-attenders [170].

The benefit of screening in reducing PCa-specific mortality (PCSM), and the even more favourable impact on metastases rates is counterbalanced by the side effects of screening, such as increased diagnosis rates, which has led to overtreatment of low-risk PCa, and subsequent treatment-related side effects [171]. Regarding QoL, the beneficial effects of screening and the side effects appear to balance out, resulting in limited overall impact on the invited population [171, 172].

All of the screening studies presented above were conducted in the pre-MRI era, with a PSA-based threshold for biopsy, and only systematic biopsies. Recognition of the harms of overdiagnosis and overtreatment had led to a redesign in the pathway for early detection of PCa including identification of specific risk groups, individualised retesting interval, improved indication for biopsy using risk calculators and/or MRI, targeted biopsies, and the application of AS for low-risk disease.

An SR concluded that integrating MRI in PCa screening pathways is associated with a reduction in the number of unnecessary biopsies and overdiagnosis of insignificant PCa, while maintaining csPCa detection as compared with PSA-only screening [173]. There are a number of ongoing screening studies, where MRI +/- other approaches are incorporated. The Gothenburg-2 screening study, including MRI and targeted biopsies only for men with PSA ≥ 3 ng/mL (or ≥ 1.8 ng/mL), has shown that the MRI + targeted biopsies only approach omitted more than half of csPCa, with a very low risk of missing an incurable PCa [174]. In the Stockholm3-MRI study, in which the Stockholm 3 serum test was used before MRI for repeat screening, showed comparable results with lower detection rates of csPCa, but with a reduction of number of MRIs depending on the cut-off value of the Stockholm 3 serum test (≥ 0.11 or ≥ 0.15) [175]. Other ongoing screening trials are the Finish ProScreen trial, where a 4-kallikrein panel risk score was used before MRI, and the German PROBASE study on screening of younger men (from the age of 45); however, the data from these studies remain preliminary at this point in time [176, 177]. An SR also concluded that risk-based screening followed by MRI testing seemed to be more cost-effective than no screening [178].

After a negative screening, PSA measurement must be repeated as long as life expectancy remains favourable [179], but the optimal intervals for PSA follow-up are unknown, as they varied between several prospective screening trials. A risk-adapted strategy might be a consideration, based on the initial PSA level. Men with a baseline PSA < 1ng/mL at 40 years or < 2ng/mL at 60 years are at decreased risk of PCa metastasis or death from PCa several decades later [48, 156]. The retesting interval can therefore be every two years for those initially at increased risk or postponed up to eight years for those at low risk [156, 180].

An analysis of ERSPC data supports a recommendation for an eight-year screening interval in men with an initial PSA concentration < 1ng/mL. Fewer than 1% of men with an initial PSA concentration < 1ng/mL were found to have a concentration above the biopsy threshold of 3ng/mL at four-year follow-up. The cancer detection rate by eight years was close to 1% [181]. The long-term survival and QoL benefits of extended PSA retesting (every eight years) remain to be proven at a population level.

5.1.4 ***Screening in patients with BRCA mutations***

The IMPACT study evaluates targeted PCa screening using PSA in men aged 40-69 years with germline *BRCA1/2* mutations (annually, biopsy recommended if PSA > 3.0ng/mL). After three years of screening, *BRCA2* mutation carriers were associated with a higher incidence of PCa, a younger age of diagnosis, and more clinically significant tumours compared with noncarriers [151, 182]. The influence of *BRCA1* mutations on PCa remained unclear. No differences in age or tumour characteristics were detected between *BRCA1* carriers and *BRCA1* noncarriers. The mismatch repair cohort of IMPACT in men with *MSH2* and *MSH6* pathogenic variants found a higher incidence of significant PCa versus noncarriers [183]. The uncertainties in the benefits to harm ratio for screening also applies in the group.

5.1.5 ***Genetic testing for inherited prostate cancer***

Increasing evidence supports the implementation of genetic counselling and germline testing in early detection and PCa management [184]. Several commercial screening panels are now available to assess the main PCa risk genes [185]. However, it remains unclear when germline testing should be considered and how this may impact localised and metastatic disease management. Germline *BRCA1* and *BRCA2* mutations occur in approximately 0.2% to 0.3% of the general population [27, 186]. It is important to understand the difference between somatic testing, which is performed on the tumour, and germline testing, which is performed on blood or saliva and identifies inherited mutations. Genetic counselling is required prior to and after undergoing germline testing. Somatic testing should be considered for all patients presenting with metastatic PCa and fit enough to consider a PARPI.

Germline mutations can drive the development of aggressive PCa. Therefore, the following men, with a family history of high-risk germline (DNA repair gene) mutations or a family history of multiple cancers on the same side of the family should be considered for germline testing:

- Men with BRCA mutations on somatic testing.
- Men with metastatic PCa who are candidates for targeted treatment.
- Men with multiple family members diagnosed with csPCa at age < 60 years or a family member who died from PCa.

5.2 Diagnostic tools

Various diagnostic tools are available for the diagnosis of prostate cancer (PCa). These tools can be used separately, or in multi-tier combinations and/or sequences. Usually, diagnosis is confirmed histopathologically using prostate biopsy.

*5.2.1 **Digital rectal examination***

In approximately 18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level [187]. A suspect DRE in patients with a PSA level ≤ 4ng/mL has a positive predictive value (PPV) of 5-30% [187]. In the ERSPC trial screening setting, an abnormal DRE in conjunction with an elevated PSA more than doubled the risk of a positive biopsy (48.6% vs. 22.4%) [188]. Abnormal DRE is an indication for MRI, or direct biopsy in case of suspicion of extracapsular disease (cT3-4) [188, 189]. An abnormal DRE is associated with an increased risk of a higher ISUP GG (GG), predicts clinically significant PCa in men under active surveillance (AS) [190] and remains a strong predictor of advanced PCa (OR: 11.12 for cT3 and OR: 5.28 for cT4) [191]. Clinical T staging, as well as current EAU risk group stratification, depends on DRE.

*5.2.2 **Prostate-specific antigen***

Prostate-specific antigen is a glycoprotein enzyme secreted by prostate epithelial cells with a small portion present in the blood stream. It is the primary test when there is a suspicion of PCa. Its use as a serum marker has revolutionised PCa diagnosis [192]. Prostate-specific antigen is organ-specific but not cancer-specific; therefore, it may also be elevated in BPH, prostatitis and other non-malignant conditions. There are no agreed standards for defining abnormal PSA thresholds [193]. It is a continuous parameter, with higher levels indicating greater likelihood of PCa. Rarely some men may harbour PCa despite having low serum PSA [194].

In a screening situation, the most frequently applied threshold for PSA is ≥ 3.0ng/mL, resulting in 16.5% of invited men returning a positive test [195]. Due to differences in cancer prevalence, protocol for referral, and diagnostic algorithm, the risk of finding PCa at a specific PSA threshold in a clinical cohort may be different than in a screening situation. Prostate-specific antigen retains its diagnostic value for cancer detection in symptomatic/referred patients. A review and meta-analysis on the diagnostic accuracy of PSA (≥ 4.0ng/mL) for the detection of PCa in clinically referred men found an estimated combined sensitivity of 0.93 and specificity of 0.20 [196].

Prostate-specific antigen production is androgen--dependent and 5α-reductase inhibitors (e.g. finasteride, dutasteride), used for benign prostatic enlargement of the prostate, reduce PSA levels by 50% [197]. In such cases, PSA level should be corrected to decide on further investigation, although PSA density is less impacted because prostate volume decreases concomitantly.

In case of a moderately elevated PSA, a repeat test after a few weeks should be considered to confirm the indication for further diagnostic analysis, because one-third of men with a PSA < 10ng/mL had a difference of greater than +/- 1.0ng/mL at the second measurement [198]. Within 1-2 months, PSA drops to below 3ng/mL in approximately one-fifth of men.

A repeat PSA test before prostate biopsies in men with an initial PSA 3-10ng/mL reduced the indication for biopsies in 16.8% of men while missing 5.4% ISUP GG > 1 in the Stockholm3 trial [199]. Similarly, in the Prostate Testing for Cancer and Treatment (ProtecT) trial, men with a more than 20% lower repeat-PSA analysis within seven weeks had a lower risk of PCa (OR: 0.43, 95% CI: 0.35-0.52), as well as a lower risk of ISUP GG ≥ 2 (OR: 0.29, 95% CI: 0.19-0.44) [200]. Based on the above, a PSA of 3-10ng/mL in men without suspicious findings on palpation should prompt a second PSA test after four weeks. If the PSA has normalised, a new PSA test can be performed after one year.

Repeat PSA should be performed in the same laboratory using the same assay under standardised conditions (i.e. no ejaculation, manipulations and urinary tract infections [UTIs]) [201, 202]. The type of PSA assay used may impact PSA values and rates of PSA above certain fixed thresholds [203]. Table 5.2 presents sources of error in PSA value assessment.

Table 5.3: Sources of error in PSA value assessment

Sources of error in PSA value assessment
• Intraindividual variation: PSA values can vary by +/- 15% [204]. • Measurement method: Variations exist between laboratories (up to approximately 5%). • Sample handling: Proper handling is crucial, with specific stability timelines for centrifuged samples. • (Febrile) urinary tract infection: Infections can cause very high PSA values (> 100ng/mL), taking up to a year to normalise [205, 206]. • Acute urinary retention: This condition moderately increases PSA values [207]. • Biopsy: PSA tests should be delayed for at least a month after biopsies [208]. • Hypogonadism: PSA production depends on testosterone levels, affecting PSA values in men with low testosterone [209, 210]. • Prostate-specific antigen production is androgen-dependent and 5α-reductase inhibitors (e.g. finasteride, dutasteride), used for benign prostatic enlargement of the prostate, reduce PSA levels by 50% [197]. • Digital rectal examination does not affect PSA value [211].

*5.2.3 **Prostate-specific antigen density***

Prostate-specific antigen density (PSA-D) is the level of serum PSA divided by the prostate volume. The higher the PSA-D, the more likely clinically significant PCa is present; particularly in smaller prostates when a PSA-D cut-off of 0.15ng/mL/cc was applied [195]. Several studies found a PSA-D over 0.1-0.15ng/mL/cc predictive of PCa [212, 213]. Patients with a PSA-D below 0.09ng/mL/cc were found unlikely (4%) to be diagnosed with csPCa [214]. PSA-D is also one of the strongest predictors incorporated in risk calculators for biopsy decisions [215].

PSA-D based on volume estimation assessed by DRE is imperfect due to an underestimation of prostate volume [216]. A lack of standardisation of prostate volume estimation exists in imaging-based prostate volume estimation as TRUS or MRI use various techniques such as ellipsoid formula or planimetry. Nonetheless, one study involving seven radiologists who assessed prostate volume on 40 MRI scans using two different ellipsoid methods and a manual planimetry method suggested that intra- and inter-reader reproducibility of the three methods were excellent with intraclass correlation coefficient > 0.90 [217]. In a series of 640 men, TRUS found prostate volumes on average 8% smaller than MRI. In the 109 men who underwent RP, MRI-derived prostate volume was better correlated to the volume of the surgical specimen than TRUS-derived volume [218].

Transabdominal ultrasound evaluation of prostate volume leads to an overestimation of the prostate volume by 9.9mL [219].

PSA-D remains predictive for csPCa when combined with MRI PIRADS scores [220, 221].

*5.2.4 **Magnetic resonance imaging***

5.2.4.a ***Diagnostic performance***

Prostate MRI combines several imaging sequences to identify PCa accurately. MRI is initiated upon suspicion of PCa based on PSA and/or DRE. In addition to suggesting the presence of PCa, imaging also enables guidance in targeted prostate biopsy and provides staging information.

Prostate cancer appears as areas with low signal intensity on T2-weighted imaging, restriction of diffusion on diffusion-weighted imaging, and early and intense enhancement on dynamic contract enhanced imaging. However, there is substantial overlap between the appearances of PCa and some prostate benign conditions.

Correlation with RP specimens shows good sensitivity for MRI in the detection and localising of ISUP GG ≥ 2 cancers, especially when their diameter is larger than 10mm. MRI is less sensitive in identifying ISUP GG 1 PCa [222-225]. The good sensitivity of MRI for ISUP GG ≥ 2 cancer was further confirmed in patients who underwent template biopsies. In a Cochrane meta-analysis comparing MRI to template biopsies (≥ 20 cores) in biopsy-naive and repeat-biopsy settings, MRI had a pooled sensitivity of 0.91 (95% CI: 0.83-0.95) and a pooled specificity of 0.37 (95% CI: 0.29-0.46) for ISUP GG ≥ 2 cancers. For ISUP GG ≥ 3 cancers, MRI-pooled sensitivity and specificity were 0.95 (95% CI: 0.87-0.99) and 0.35 (95% CI: 0.26-0.46), respectively [226].

The Prostate Imaging-Reporting and Data System (PI-RADS) standardises interpretation and stratifies patients with suspected PCa on a 1- to 5- risk scale of having csPCa, where patients with a PI-RADS 3-5 lesion are considered at risk of csPCa and, therefore, may be candidates for MRI-targeted prostate biopsy. The PI-RADS document has been revised twice, and version 2.1 is currently used [227, 228].

A meta-analysis of PI-RADS v2.1 that used transrectal or transperineal biopsy data findings as reference, found that ISUP GG ≥ 2 cancer detection rates at patient level were 6% [95% CI: 3-12%] for PI-RADS 1, 6% [3-11%] for PI-RADS 2, 20% [15-26%] for PI-RADS 3, 55% [45-65%] for PI-RADS 4, and 83% [78-88%] for PI-RADS 5 [229]. The median prevalence for csPCa was 43%. Of note, the cancer detection rates are positive predictive values and, as such, depend on prevalence.

In another meta-analysis, the median cancer detections rate was also 6% for PI-RADS 1-2 categories, but varied from 3% when the PSA density (PSA-D) was below 0.10 ng/mL to 18% when the PSA-D was above 0.20 ng/mL. PSA-D also allowed risk stratification of PI-RADS 3 and 4-5 categories (see Table 5.5) [230].

Most MRI histological correlations [231], but not all [232], suggest that visibility at MRI is associated with molecular hallmarks of aggressiveness, and thus, that MRI-invisible cancers could harbour a better prognosis. Similarly, although preliminary studies suggested that cancers with intraductal/cribriform patterns were MRI-invisible, larger series showed that these aggressive patterns were MRI-visible in more than 95% of the cases and tended to be associated with high PI-RADS scores [233, 234].

5.2.4.b Image quality and inter-reader reproducibility

Quality assurance and quality control programs are crucial for improving image quality and reducing diagnostic errors. Image quality has substantial impact on MRI performance [235] and most discrepancies between MRI and biopsy results may be explained by suboptimal image quality and basic mistakes in interpretation [236]. Guidelines standardise patient preparation and imaging protocols [228, 235, 237]. The prostate image quality (PI-QUAL) score provides simple criteria to assess image quality and decides when to repeat the examination [238] and is a convenient tool to follow improvements in quality [239].

Despite the use of the PI-RADS scoring system, MRI inter-reader reproducibility remains moderate at best. MRI performance is better with experienced radiologists and at high-volume centres, which currently limits its broad use by non-dedicated radiologists [237, 240]. Certification programs are being developed in Europe to improve image and interpretation quality through continuous education, outcome audits and feedback via peer review [241]. Interdisciplinary cooperation with pathological correlation and feedback is also crucial to improving MRI interpretation [242, 243].

5.2.4.c *Circumstances for biparametric MRI*

The steadily increasing demand for diagnostic prostate MRI has led to concerns regarding the lack of access to and the availability of qualified MRI scanners and sufficiently experienced radiologists, radiographers, and technologists to meet the demand. Solutions must enhance operational benefits without compromising diagnostic performance, quality, and delivery of service. Solutions should also mitigate risks such as decreased reader confidence and referrer engagement. One approach may be the implementation of MRI without the use gadolinium-based contrast medium (biparametric MRI), but only if certain prerequisites such as high-quality imaging, expert interpretation quality, and availability of patient recall are mandated [241]. Alternatively, or in combination, a clinical risk-based approach could be used for protocol selection, specifically, which biopsy-naive men need MRI with contrast medium (multiparametric MRI). Similar diagnostic accuracies have been shown between both approaches in several meta-analyses [244-246]; however, conclusions were based on retrospective analyses of single-centre data and small sample sizes, in which decisions were made on multiparametric MRI, rather than biparametric (non-contrast) MRI.

The PRIME study, was a prospective, multicentre, within-patient, noninferiority trial of 490 biopsy-naive patients with clinical suspicion of PCa (elevated PSA level and/or abnormal DRE findings) from 22 centres [247]. A positive MRI was defined as Likert suspicions scores 3 to 5. Results were consistent when using the PI-RADs v2.1 instead of the Likert scoring system. Biparametric MRI was noninferior to multiparametric MRI, detecting GG ≥ 2 cancers in 29.2%, compared with 29.6% (difference, −0.4% [95% CI: −1.2 to 0.4], p = 0.50). Biparametric and multiparametric MRI showed a sensitivity of 98.0% (95% CI: 94.2-99.6) and 99.3% (95% CI: 96.3-100.0) and a specificity of 61.6% (95% CI: 56.1-66.8) and 60.1% (95% CI: 54.6-65.4), respectively. Biparametric MRI detected ISUP GG 1 cancers in 9.2%, compared with 9.6% with the use of multiparametric MRI (difference, −0.4% [95% CI: −1.2 to 0.4]). Central quality control demonstrated that 99% of scans were of adequate diagnostic quality.

The PI-CAI Consortium conducted a retrospective non-inferiority observer study of 400 biopsy-naive patients with clinical suspicion of PCa (elevated PSA level and/or abnormal DRE findings) from four European centres [248]. A positive MRI was defined as PI-RADS scores 3-5. Biparametric MRI was noninferior to multiparametric MRI, detecting ISUP GG ≥ 2 cancers in 29.3%, compared with 29.5%. Biparametric MRI detected ISUP GG 1 cancers in 9.8%, compared with 10.0% with the use of multiparametric MRI. Biparametric MRI was noninferior

to multiparametric MRI in AUROC (difference of -0.6% [95% CI; -1.2 to 0.1], p < 0.001), sensitivity (difference of -0.9% [95% CI: -1.7 to 0.0], p < 0.001) and specificity (difference of 0.9% [95% CI: 0.0-1.8], p < 0.001). The study's cohort exhibited a wide range of image quality, where the majority (65%) achieved an overall PI-QUAL score of 2-3 in multiparametric MRI scans.

The PI-RADS recommendations (2021) on the use of biparametric MRI in some circumstances are still valid, but only if certain prerequisites such as high-quality imaging, expert interpretation quality, and availability of patient recall are mandated [241].

5.2.4.d Quantitative approaches and artificial intelligence

As the PI-RADS criteria remain subjective, approaches using quantitative thresholds for imaging biomarkers (e.g. the apparent diffusion coefficient or enhancement parameters) have been proposed [249]. However, there is still a large variability in these biomarker values across suppliers, MRI scanners and imaging protocols, which currently makes them difficult to be widely used [250-252].

The integration of artificial intelligence (AI)-based algorithms into prostate MRI workflows may address the limitations associated with single-reader interpretations, such as intra- and inter-reader variability and diagnostic errors, and may also improve reading times [253]. AI-based algorithms as standalone have recently provided excellent results in detecting ISUP GG ≥ 2 PCa on MRI and can even outperform experienced human readers [254-258]. However, AI algorithms tend to show decreased performance when tested on images from a different vendor or acquired with different image parameters as compared to their training dataset [259]. It is therefore essential to test them on external cohorts to assess their generalisability [260]. To date, only a few AI systems have been assessed on truly external multicentric cohorts [261]. Two prospective studies have tested AI algorithms on external cohorts. In one, the AI system had lower sensitivity 87.6% (95% CI: 79.4-93.4) versus 99% (95% CI: 94.4-100); p=0.005) but higher specificity 64.8% (95% CI: 55-73.8) verses 31.3% (95% CI: 14-30.2; p < 0.001) than human reading [257]. In the other, the algorithm detected csPCa missed by human reading in 4% of patients, but at the expense of a doubling of the false positive rate (0.66 vs. 1.39) [262].

Additionally, the complex dynamics of human-AI interaction and the potential AI-integrated workflow strategies (e.g. using AI as a triage tool, a decision support or an independent second reader) warrant further investigation [253].

5.2.5 Ultrasound-based techniques

5.2.5.a Transrectal ultrasound (TRUS)

Standard TRUS is not reliable for detecting PCa [263] and the diagnostic yield of additional biopsies performed on hypoechoic lesions is negligible [264]. Artificial intelligence algorithms trained to detect PCa on TRUS images have shown promising preliminary results, but confirmation of these results in independent cohorts is required.

5.2.5.b Micro-ultrasound

High-resolution micro-ultrasonography (micro-US) operates at 29 MHz with a spatial resolution of 70 microns. This allows, in theory, the visualisation of normal prostate ducts and of PCa foci that alter the ductal architecture. The Prostate Risk Identification using Micro-UltraSound (PRI-MUS) score assessed the risk of malignancy for focal lesions, with scores of 1-2 considered low-risk, 3 equivocal, and 4-5 suspicious [265].

Two prospective trials assessed MRI and micro-US interpreted in a blinded manner before combined targeted and systematic biopsy. In one, MRI and micro-US detected 60 (76%) and 58 (73%) of the 79 csPCa, respectively, while systematic sampling detected 45/79 cases (57%). MRI-targeted biopsy detected seven csPCa missed by micro-US, three of which were anterior lesions. Micro-US-guided biopsy detected five csPCa missed by MRI, three of which were at the apex [266]. In the other study, MRI- and micro-US-targeted biopsy depicted csPCa in 37 (39%) and 33 (35%) of the 94 men, respectively, while the MRI- plus micro-US-targeted pathway detected 38 csPCa [267]. These findings suggest that MRI and micro-US could complement each other. Micro-US could also be an interesting alternative to MRI/US fusion allowing direct targeting of MRI lesions and potential detection of additional suspicious lesions. However, this technique has limitations which should be acknowledged. Because of the use of high-frequency ultrasound with low(er) wave penetration, the transrectal visualisation of the anterior part of large prostates remains suboptimal. In a series of 92 PI-RADS ≥ 3 lesions in the transition zone, 21 (23%) were invisible on micro-US, even when the operator was aware of the MRI results [268]. In a prospective trial involving six experienced readers, sensitivity for ISUP GG ≥ 2 PCa increased from 0.66±0.05 to 0.87±0.09 when cases with anterior tumours were excluded [269]. Micro-US may also generate a substantial proportion of false positive findings. In one prospective trial, the percentages of csPCa were similar in men with positive micro-US and in those with positive MRI findings (41% vs. 39%) [266]. However, in another study,

micro-US detected 33 csPCa by sampling 162 suspicious lesions (10% of patients with micro-US negative findings [PRIMUS 1-2]), while MRI detected 38 csPCa while sampling 93 lesions (34% of patients with MRI-negative findings (PI-RADS 1-2) [267]. In a recent RCT, the percentage of patients with negative findings was 20% (71/347) for micro-US versus 32% (179/557) for MRI [270]. Finally, micro-US interoperator variability has rarely been evaluated. In a prospective series of 57 patients, the light's kappa value for localising the lesions across six experienced readers was only 0.30 (95% CI: 0.21-0.39) [269].

Since most available data were obtained at high-volume well-trained centres, a learning curve and a volume effect on quality outcomes similar to what was observed after the introduction of MRI is expected.

5.2.5.c Other ultrasound-based methods

Colour-Doppler, sonoelastography or contrast-enhanced US provided promising preliminary findings, either alone, or combined into the so-called 'multi-parametric US' [271, 272]. In the multi-parametric US versus multi-parametric MRI to diagnose PCa (CADMUS) trial, 306 patients underwent both multi-parametric MRI and multi-parametric US composed of B-mode, Colour Doppler, real-time elastography, and contrast-enhanced US. Patients with at least one positive test underwent targeted biopsy. Multi-parametric US detected 4.3% fewer csPCa while submitting 11.1% more patients to biopsy than MRI [273].

5.2.6 Prostate-specific membrane antigen-positron emission tomography/computed tomography

Though mainly used for staging purposes, hybrid radiolabelled PSMA-PET imaging (i.e., PET/CT or PET/MRI) may be used to indicate the precise location for targeted biopsies, as well as to follow candidates in active surveillance setting. For csPCa detection, a pooled sensitivity of 0.89 and a pooled specificity of 0.56 have been reported [274].

In a prospective trial of 291 patients, combined PSMA PET + MRI improved negative predictive value (NPV) compared with MRI alone (91% vs. 72%, test ratio = 1.27 [1.11-1.39], $p < 0.001$). Sensitivity also improved (97% vs. 83%, $p < 0.001$), but specificity was reduced (40% vs. 53%, $p = 0.011$) [136]. The PRIMARY score was shown to be valid only when using harmonised PET cameras and the same PSMA PET ligands [136]. A *post hoc* analysis of the PRIMARY study evaluated the clinical significance of patterns of intraprostatic PSMA activity, proposing a five-point score to optimise the accuracy of radiolabelled-PSMA PET/CT for csPCa. Key patterns used within the PRIMARY score demonstrated an improved specificity and diagnostic accuracy for the detection of csPCa. Sensitivity, specificity, PPV, and NPV for a PRIMARY score of 1 or 2 (low-risk patterns) versus a PRIMARY score of 3-5 (high-risk patterns) were 88%, 64%, 76%, and 81%, respectively, compared with 83%, 53%, 69%, and 72%, respectively, for a PI-RADS score of 2 versus 3-5 on mpMRI [275].

A composite P score combining MRI and PRIMARY score was proposed for more accurate diagnosis of csPCa [276]. The Standardised Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Analysis and Reporting Consensus (SPARC) project offers the adoption of harmonised and reproducible frameworks for reporting of PSMA PET/CT, including molecular imaging (mi) for PSMA expression, miTNM PROMISE classification for reporting of PSMA PET/CT, the PRIMARY score for intraprostatic staging, PSMA volume, mean standardised uptake value (SUV_{mean}), and maximum standardised uptake value (SUV_{max}) [277].

A systematic review and meta-analysis focusing on the role of PSMA PET for PCa diagnosis and primary staging before definitive treatment revealed good accuracy for intraprostatic diagnosis and staging, with a sensitivity, specificity, PPV, and NPV of PSMA PET for csPCa of 82% (95% CI: 73-90%), 67% (95% CI: 46-85%), 77% (95% CI: 63-88%), and 73% (95% CI: 56-87%), respectively [278].

5.2.7 Blood and urine biomarkers

Urine and serum biomarkers, as well as tissue-based biomarkers, have been proposed for improving detection and risk stratification of PCa patients, potentially avoiding unnecessary biopsies and/or unnecessary imaging. However, their efficacy has not been validated [279].

5.2.7.a Blood based biomarkers: PHI/4K score/IsoPSA/Stockholm3/Proclarix

The use of biomarkers (included in a nomogram) may help in predicting indolent PCa [280, 281]. Several assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the United States Food and Drug Administration (FDA)- approved Prostate Health Index (PHI) test (combining free and total PSA and the [-2]pro-PSA isoform [p2PSA]), and the four kallikrein (4K) score test (measuring free, intact and total PSA and kallikrein-like peptidase 2 [hK2] in addition to other parameters, such as age, DRE and prior biopsy status). Both tests are intended to reduce the number of unnecessary prostate biopsies in PSA-tested men. Several

prospective multicentre studies demonstrated that both the PHI and 4K score test outperformed f/t PSA for PCa detection, with an improved prediction of csPCa in men with a PSA between 2-10ng/mL [282, 283]. In a head-to-head comparison both tests performed equally [284].

In contrast to the 4K score and PHI, which focus on the concentration of PSA isoforms, IsoPSA utilises a technology which focuses on the structure of PSA. In a multicentre prospective validation in 271 men, the assay area under curve (AUC) was 0.784 for high-grade versus low-grade cancer/benign histology, which was superior to the AUCs of total PSA and percent free PSA [208]. In men with a negative mpMRI, PSA-D, 4K score and family history predicted the risk of csPCa on biopsy and using a nomogram reduced the number of negative biopsies and indolent cancers by 47% and 15%, respectively, while missing 10% of csPCa [285].

The Stockholm3 test is a prediction model that is based on several clinical variables (age, first-degree family history of PCa, and previous negative biopsy), blood biomarkers (total PSA, f/t PSA, human kallikrein 2, macrophage inhibitory cytokine-1, and *microseminoprotein*-β [MSMB]), and a polygenic risk score for predicting the risk of PCa with ISUP GG ≥ 2, and was shown to reduce the percent of clinically insignificant cancers when used in combination with MRI in a PSA screening population [286]. It also has the potential to decrease the number of mpMRI scans required in prostate cancer screening [287].

The Proclarix® test is a blood-based test that estimates the likelihood of csPCa according to measurement results for thrombospondin-1, cathepsin D, total PSA, percentage free PSA and patient age. This test has been correlated with the detection of csPCa, notably in case of equivocal MRI (PI-RADS 3 lesions) [288].

5.2.7.b Urine biomarkers: PCA3/SelectMDX/MyProstateScore (MPS/MPS2)/ExoDX

Prostate cancer gene 3 (*PCA3*) is an overexpressed long non-coding RNA (lncRNA) biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. However, the clinical utility of the commercially available Progensa urine test for *PCA3* for biopsy decision-making remains unclear. Still, combining MRI findings with the *PCA3* score may improve risk stratification [289].

The SelectMDX test is similarly based on mRNA biomarker isolation from urine. The presence of *HOXC6* and *DLX1* mRNA levels is assessed to provide an estimate of the risk of both presence of PCa on biopsy as well as presence of high-risk cancer [290]. A multi-centre trial evaluated SelectMDX in men with an MRI PI-RADS score < 4 or PI-RADS score < 3, and the percentage of missed csPCas was 6.5% and 3.2%, respectively, whereas 45.8% and 40% of biopsies were avoided [291]. Hendriks *et al.* found more biopsies were avoided and more high-grade PCas detected in an MRI-based biopsy strategy compared to a SelectMDX strategy. When both tests were combined, more Gleason grade > 1 lesions were found, but the number of negative or low-grade cancer biopsies more than doubled [281]. Combining SelectMDX and MRI in men with a PSA between 3-10ng/mL had a negative predictive value (NPV) of 93% [292]. The clinically added value of SelectMDX in the era of upfront MRI and targeted biopsies remains unclear [293].

TMPRSS2-ERG fusion, a fusion of the transmembrane protease serine 2 (*TMPRSS2*) and the *ERG* gene can be detected in 50% of PCas [294]. When detection of *TMPRSS2-ERG* in urine was added to PCA3 expression and serum PSA (MyProstateScore [MPS]), cancer prediction improved [295]. An update of the test, MyProstateScore 2.0 (MPS2), in which an 18-gene score was used, outscored the original MPS model significantly [296]. Exosomes secreted by cancer cells may contain mRNA diagnostic for high-grade PCa [297, 298]. Use of the ExoDx Prostate IntelliScore urine exosome assay resulted in avoiding 27% of unnecessary biopsies when compared to standard of care (SOC). However, both the MiPS score and ExoDx assay are currently considered investigational.

In the screening population of the ERSPC study, the use of both *PCA3* and 4K panel when added to the risk calculator led to an improvement in AUC of less than 0.03 [299]. Based on the available evidence, some biomarkers could help in discriminating between aggressive and nonaggressive tumours with an additional value compared to the prognostic parameters currently used by clinicians [300]. However, upfront MRI is also likely to affect the utility of the above-mentioned biomarkers.

A review of the different biomarkers, used individually and in combination, concluded that although the results from the various urine-based biomarker tests were promising no one specific test could be recommended for clinical practice at present [301].

*5.2.8 Recommendations for individual early detection and germline testing**

Recommendations	Strength rating
Offer an individualised risk-adapted strategy for early detection to well-informed males with a life expectancy of at least 15 years.	Weak
Offer early prostate-specific antigen (PSA) testing to well-informed men at elevated risk of having PCa: • males from 50 years of age; • males from 45 years of age and a family history of PCa < 60 years; • males of African descent from 45 years of age; • males carrying breast cancer gene 2 (*BRCA2*) mutations from 40 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: • males with a PSA level of > 1 ng/mL at 40 years of age; • males with a PSA level of > 2ng/mL at 60 years of age. Postpone follow-up for up to eight years in those not at risk.	Weak
Stop early diagnosis of PCa based on life expectancy and performance status. Males who have a life expectancy of less than 15 years are unlikely to benefit.	Strong
In asymptomatic males with a PSA level between 3 and 10 ng/mL initially repeat PSA testing prior to further investigations.	Weak
In asymptomatic males with a PSA level between 3 and 20 ng/mL use one of the following tools for biopsy indication: • magnetic resonance imaging of the prostate.	Strong
• risk calculator, provided it is correctly calibrated to the population prevalence. • an additional serum or urine biomarker test.	Weak
Germline testing*	
Advise germline testing in patients with multiple family members diagnosed with PCa at age < 60 years or a family member who died from PCa < 60 years.	Weak
Offer germline testing in patients with a family history of high-risk germline mutations or a family history of multiple cancers on the same side of the family.	Strong
Offer germline testing to patients with *BRCA* mutations on somatic testing.	Strong

**Genetic counselling is required prior to germline testing.*

5.3 Pathology of prostate needle biopsies

5.3.1 Processing

Prostate needle core biopsies from various sites are processed separately, as delivered by the biopsy operator. Before processing, the number and length of the cores are recorded. The length of biopsy tissue significantly correlates with the PCa detection rate [302]. If individual cores can clearly be identified in submitted jars, a maximum of three cores should be embedded per tissue cassette, and sponges or paper should be used to keep the cores stretched and flat to achieve optimal flattening and alignment [303, 304]. To optimise detection of small lesions and improve accuracy of grading, paraffin blocks should be cut at three levels and intervening unstained sections may be kept for immunohistochemistry (IHC) [305].

5.3.2 Microscopy and reporting

Diagnosis of PCa is based on histology. The diagnostic criteria include features pathognomonic of cancer, major and minor features favouring cancer and features against cancer. Ancillary staining and additional (deeper) sections should be considered if a suspect lesion is identified [305]. Diagnostic uncertainty is resolved by intradepartmental or external consultation [305]. Sections 5.3.2.a and 5.3.2.b list the recommended terminology and item list for reporting prostate biopsies [304]. Type and subtype of PCa should be reported, such as acinar adenocarcinoma, ductal adenocarcinoma and small or large cell neuroendocrine carcinoma, even if representing a small proportion of the PCa. The distinct aggressive nature of small/large cell neuroendocrine carcinoma should be commented upon in the pathology report [304]. In addition to grading acinar and ductal adenocarcinoma, the percentage of Gleason grade 4 component should be reported in Gleason score 7 (3+4 and 4+3) PCa biopsies. Percentage Gleason grade 4 has additional prognostic value and is considered in some AS protocols [306, 307]. Data suggest that the amount of Gleason grade 3 and 4 proportion have no additional impact on adverse pathology, once Gleason grade 4's absolute volume is known. Biopsy Gleason grade 4 length has predictive value for adverse pathology and BCR-free survival, and may have better discriminative value than

Gleason grade 4 percentage [308-310]. However, further studies comparing the performance of Gleason grade 4 length and percentage and establishing clinically useful cut-offs are needed. Considerable evidence has been accumulated in recent years supporting the idea that, among the Gleason grade 4 patterns, cribriform pattern carries an increased risk of biochemical recurrence, metastatic disease and death from disease [311-314]. Reporting of this sub-pattern based on established criteria is recommended [118, 315]. Intraductal carcinoma, defined as an extension of cancer cells into pre-existing prostatic ducts and acini, distending them, with preservation of basal cells [118], should be distinguished from high-grade prostatic intraepithelial neoplasia (PIN) [316] as it conveys unfavourable prognosis in terms of biochemical recurrence and cancer-specific survival (CSS) [317, 318]. Its presence should be reported whether occurring in isolation or associated with adenocarcinoma [118]. Some intraepithelial lesions have architectural complexity and/or cytological atypia exceeding those of high-grade PIN but fall short for a definitive diagnosis of IDC. These lesions are referred to as Atypical Intraductal Proliferation (AIP) and amongst others encompass lesions that were previously classified as cribriform high-grade PIN. Small retrospective series suggest that AIP at biopsy is associated with unsampled IDC [319, 320]. Therefore, presence of AIP should be reported and commented on in non-malignant biopsies and biopsies with ISUP GG 1 and 2 cancers in the absence of overt invasive cribriform and IDC [321].

Prostatic intraepithelial neoplasia (PIN) is considered to be the precursor of PCa, and is microscopically categorised as low- or high-grade PIN. Since low-grade PIN has low reproducibility and lacks predictive value for PCa, it should not be reported. The clinical impact of high-grade PIN is unknown, specifically its predictive value for clinically significant PCa in the MRI era [321]. Atypical small acinar proliferations (ASAP) suspicious for PCa are detected in < 5% of prostate biopsies. A SR and meta-analysis, from the pre-MRI era, showed that repeat biopsies had PCa in 31% with a pooled incidence of 12% csPCa. The incidence of csPCa was lower for repeat biopsies taken within six months than for those taken after more than six months [322].

5.3.2.a **Recommended terminology for reporting prostate biopsies** [323]

Benign/negative for malignancy - if appropriate, include a description
Active inflammation
Granulomatous inflammation
High-grade prostatic intraepithelial neoplasia (PIN)
High-grade PIN with atypical glands, suspicious for adenocarcinoma
Focus of atypical glands/lesion suspicious for adenocarcinoma/atypical small acinar proliferation, suspicious for cancer
Adenocarcinoma, provide type and subtype, and presence or absence of cribriform pattern
Atypical intraductal proliferation (AIP), suspicious for intraductal carcinoma
Intraductal carcinoma

Each biopsy site should be reported individually, including its location (in accordance with the sampling site) and histopathological findings, which include the histological type and the 2019 ISUP GG [118, 324, 325]. For MRI-targeted biopsies consisting of multiple cores per target, the aggregated (or composite) ISUP GG should be reported per targeted lesion [118]. If the targeted biopsies are negative, presence of specific benign pathology should be mentioned, such as dense inflammation, fibromuscular hyperplasia or granulomatous inflammation [118, 326]. Reporting a global ISUP GG comprising all systematic (nontargeted) and targeted biopsies in conjunction to the GG per biopsy site is optional. The global ISUP GG takes into account all biopsies positive for carcinoma by estimating the total extent of each Gleason grade present. For example, if three biopsy sites are entirely composed of Gleason grade 3 and one biopsy site is composed of Gleason grade 4 only, the global ISUP GG would be 2 (i.e. GS 7[3+4]) or 3 (i.e. GS 7[4+3]), depending on whether the extent of Gleason grade 3 exceeds that of Gleason grade 4, whereas the worst grade would be ISUP GG 4 (i.e. GS 8[4+4]). If biopsy sites have different GS, taking clinical, pathological and radiological characteristics into account is recommended for patient risk stratification and management. Neither global nor worst ISUP GG is clearly superior over the other [327]. The majority of clinical studies have not specified whether global or worst biopsy grade was taken into account. In addition to GS/ISUP GG, the presence/absence of intraductal/invasive cribriform pattern should be reported [118, 324, 325]. In addition, in biopsy GS 7 (ISUP GG 2 and 3) percentage Gleason grade 4 should be monitored at the case and/or biopsy level [118, 325]. Lymphovascular invasion (LVI), EPE and ejaculatory duct/seminal vesicle involvement must each be reported, if identified, because they carry unfavourable prognostic information [328-330]. Studies on biopsy perineural invasion (PNI) have shown variable outcome. Two systematic reviews and meta-analyses of biopsy PNI showed independent association with PSM and BCR in men who underwent RP [331, 332].

A series of studies have demonstrated that computer-assisted PCa grading AI algorithms can perform grading at the level of experienced genitourinary pathologists. These algorithms have potential in supporting grading of less experienced pathologists by reducing interobserver variability and in quantitative analyses. However, more extensive and prospective validation of these algorithms is needed for implementation in daily clinical practise [118, 324, 325, 333, 334]. The proportion of systematic (nontargeted) carcinoma-positive cores as well as the extent of tumour involvement per biopsy core correlate with the ISUP GG, tumour volume, surgical margins and pathological stage in RP specimens and predict BCR, post-prostatectomy progression and RT failure. These parameters are included in nomograms created to predict pathological stage and SV invasion after RP and RT failure [335, 336]. A pathology report should therefore provide both the number of carcinoma positive cores and the extent of cancer involvement for each core. The length in millimetres and percentage of carcinoma in the biopsy have equal prognostic impact [337].

5.3.2.b **Recommended item list for reporting prostate cancer biopsies** [118, 324, 325]

Type of carcinoma
Primary and secondary Gleason grade per biopsy site and International Society of Urological Pathology (ISUP) GG
Percentage of Gleason grade 4 in Gleason Score (GS) 7 biopsies
Presence/absence of intraductal/invasive cribriform carcinoma
Presence of Atypical Intraductal Proliferation (AIP) in intraductal/invasive cribriform-negative cases
Number of cancer-positive biopsy cores
Extent of cancer (in mm or percentage)
For MRI-targeted biopsies with multiple cores aggregate (or composite) ISUP GG per lesion
For carcinoma-negative MRI-targeted biopsy, specific benign pathology, e.g. fibromuscular hyperplasia or granulomatous inflammation
If present, lymphovascular invasion (LVI), extraprostatic extension and ejaculatory duct/seminal vesicle involvement

*5.3.3 **Tissue-based prognostic biomarker testing***

After a comprehensive literature review and several panel discussions, an American Society of Clinical Oncology (ASCO)-EAU-American Urological Association (AUA) multidisciplinary expert panel issued recommendations regarding the use of tissue-based PCa biomarkers [338]. The recommendations were limited to five commercially available tests (Oncotype Dx, Prolaris, Decipher, Decipher PORTOS and ProMark) with extensive validation in large retrospective studies and evidence that their test results might impact clinical decision-making. The selected commercially available tests significantly improved the prognostic accuracy of clinical, multivariable models for identifying men who would benefit from AS and those with csPCa requiring curative treatment, as well as for guidance of patient management after RP. Few studies showed that tissue biomarker tests and MRI findings independently improved the detection of csPCa in an AS setting, but it remains unclear which men would benefit from both tests. Decipher® test outcome has been associated with presence of intraductal/invasive cribriform carcinoma but retains independent value in multivariable analysis. Since the long-term impact of the use of these commercially available tests on oncological outcome remains unproven and prospective trials are largely lacking, the Panel concluded that these tests should not be offered routinely, but only in subsets of patients for which the test result provides clinically actionable information. This includes, for example, men with favourable intermediate-risk PCa who might opt for AS or men with unfavourable intermediate-risk PCa scheduled for RT to decide on treatment intensification with hormone therapy (HT) [339]. Since then, data from a RCT including 215 patients with intermediate risk PCa randomised to two different radiotherapy doses, and with a median follow-up of 12.8 years, showed that a Decipher® test indicating high risk proved to be prognostic for disease progression (HR 1.12), biochemical failure (HR 1.22), distant metastasis (HR 1.28) and PCSM (HR 1.45) [340]. However, because the endpoint was secondary and the study was designed for a completely different purpose, the recommendations remain unchanged until the findings have been confirmed. There are several other potential biomarkers, both on the market and in development, but the evidence to support a clinical benefit sufficient for guideline inclusion is not yet available.

*5.3.4 **Tissue samples for homologous recombination repair (HRR) testing***

Homologous recombination repair testing in the PROfound trial was conducted on archival or recent biopsy tissue from primary or metastatic disease with successful sequencing in 69% [341]. Alterations in HRR genes are relatively unchanged, comparing matched treatment-naïve diagnostic and mCRPC biopsies [342, 343].

Whereas there is no preference for the use of archival or new metastatic biopsies for HRR testing, bone biopsies might be associated with lower success rates related to decalcification of tissue [344]. Testing of circulating tumour DNA might be a good alternative if tumour tissue is not available [343, 345]. With tissue as reference, ctDNA showed 81% positive and 92% negative percentage agreement [346].

5.3.5 Histopathology of radical prostatectomy specimens

5.3.5.a Processing of radical prostatectomy specimens

Histopathological examination of RP specimens describes the pathological stage, histopathological type, grade and surgical margins of PCa. It is recommended that RP specimens be totally embedded to enable assessment of cancer location, multifocality and heterogeneity. For cost-effectiveness, partial embedding can also be considered, particularly for prostates > 60g. The most widely accepted method includes complete embedding of the posterior prostate and a single mid-anterior left and right section. Compared with total embedding, partial embedding with this method missed 5% of positive margins and 7% of EPE [347].

The entire RP specimen should be inked upon receipt in the laboratory to demonstrate the surgical margins. Specimens are fixed by immersion in buffered formalin for at least 24 hours, preferably before slicing. After fixation, the apex and the base (bladder neck) are removed and cut into sagittal/parasagittal or radial sections; the shave method is not recommended [116]. The remainder of the specimen is cut in transverse, 3-4mm sections, perpendicular to the long axis of the urethra. The resultant tissue slices can be embedded and processed as whole mounts or after quadrant sectioning. Whole mounts provide better topographic visualisation, faster histopathological examination and better correlation with preoperative imaging, although they are more time-consuming and require specialist handling. For routine sectioning, the advantages of whole mounts do not outweigh their disadvantages.

5.3.5.b Radical prostatectomy specimen report

The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (Table 5.3). As a result of the complex information to be provided for each RP specimen, the use of synoptic/synoptic-like or checklist reporting is recommended. Synoptic reporting results in more transparent and complete pathology reporting [348].

Table 5.3: Mandatory elements provided by the pathology report

Histopathological (sub)type
Type of carcinoma, e.g. conventional acinar adenocarcinoma, (small cell) neuroendocrine cell carcinoma or ductal carcinoma
Subtype and unusual variants, e.g. pleomorphic giant cell or mucinous
Histological grade
Primary (predominant) Gleason grade Secondary Gleason grade Tertiary Gleason grade (if applicable) ISUP GG Approximate percentage of Gleason grade 4 or 5 (optional)
Tumour quantitation (optional)
Percentage of prostate involved Size/volume of dominant tumour nodule
Pathological staging (pTNM)
If extraprostatic extension is present: • indicate whether it is focal or extensive; • specify sites; and • indicate whether there is seminal vesicle invasion. *If applicable, regional lymph nodes:* • location; • number of nodes retrieved; • number of nodes involved.

Surgical margins
If carcinoma is present at the margin, specify the following: • sites; • extent: focal or extensive; and • (highest) Gleason grade at margin.
Other
Presence of lymphovascular invasion Location of dominant tumour Presence of intraductal carcinoma/cribriform architecture

5.3.5.c ISUP GG in prostatectomy specimens

Grading of conventional prostatic adenocarcinoma using the Gleason system is the strongest prognostic factor for clinical behaviour and treatment response [117]. The GS is incorporated in nomograms that predict disease-specific survival (DSS) after prostatectomy [349, 350]. The ISUP GG in prostatectomy specimens is generally determined in a manner similar to that in biopsies, with a minor exception, i.e. the exclusion of minor (< 5%) high-grade components from the ISUP GG. For instance, in a carcinoma almost entirely composed of Gleason grade 3, the presence of a minor (< 5%) Gleason grade 4 or 5 component is not included in the GS (ISUP GG 1), but its presence is commented upon [118]. In case of multifocality, the ISUP GG of the index lesion (i.e. the tumour having the highest grade, stage or volume) is specified.

5.3.5.d Definition of extraprostatic extension

Extraprostatic extension is defined as carcinoma mixed with periprostatic adipose tissue, or tissue that extends beyond the prostate gland boundaries (e.g. neurovascular bundle, anterior prostate). Microscopic bladder neck invasion is considered EPE. It is useful to report the location and extent of EPE for surgical and radiological quality assurance. While extent of EPE has been associated with recurrence risk in some studies [351], a systematic review and meta-analysis did not find a statistically significant difference between focal and extensive EPE for BCR-free survival [352]. There are no internationally accepted definitions of focal or microscopic versus nonfocal or extensive EPE. Some describe focal as a few glands [353] or <1 high-power field in one, or at most two sections, whereas others measure the depth of extent in millimetres [353]. At the apex of the prostate, tumour mixed with skeletal muscle does not constitute EPE. In the bladder neck, microscopic invasion of smooth muscle fibres is not equated to bladder wall invasion, i.e. not as pT4, because it does not carry independent prognostic significance for PCa recurrence and should be recorded as EPE (pT3a) [354, 355]. Stage pT4 is assigned when the tumour invades the bladder muscle wall as determined macroscopically [109].

5.3.5.e PCa volume

Although PCa volume at RP correlates with tumour grade, stage and surgical margin status, the independent prognostic value of PCa volume has not been established [353, 356, 357]. Improvement in prostatic radio imaging enables more accurate preoperative measurement of cancer volume. Since the independent value of pathological tumour volume at RP has not been established, reporting of the diameter/volume of the dominant tumour nodule, or a rough estimate of the percentage of cancer tissue, is optional [358].

5.3.5.f Surgical margin status

Surgical margin status is an independent risk factor for BCR. Margin status is positive if tumour cells are in contact with the ink on the specimen surface. Margin status is negative if tumour cells are close to the inked surface [359] or at the surface of the tissue lacking ink. In tissues that have severe crush artefacts, it may not be possible to determine margin status [360]. Surgical margin is separate from pathological stage, and a positive margin is not evidence of EPE [361]. There is evidence of a relationship between margin extent and recurrence risk [362, 363]. A systematic review including 16 retrospective studies showed that positive surgical margin length measured either as continuous or dichotomised (< 3mm vs. > 3mm, < 1mm vs. > 1mm) variable was an independent prognostic parameter for BCR-free survival [364]. Some indication must be provided of the multifocality and extent of margin positivity, such as the linear extent in millimetres of involvement: focal, ≤ 1mm vs. extensive, > 1mm [365], or number of blocks with positive margin involvement. The Gleason score at the positive margin was found to correlate independently with outcome and should be reported [348, 362, 366].

5.3.5.g Rare aggressive PCa (sub)types

While acinar and ductal adenocarcinoma are, by far, the most common types of PCa, other rare aggressive PCa types and subtypes are recognised. Neuroendocrine transformation can occur as small cell, large cell or amphicrine (synonym: adenocarcinoma with diffuse neuroendocrine differentiation) carcinoma. (Adeno) squamous, sarcomatoid and pleomorphic giant cell carcinoma are all exceedingly rare. These (sub)types of

PCa are predominantly found in the CRPC setting, but can also occur at primary diagnosis. Respective subtypes together with adenoid cystic (basal cell) carcinoma have limited sensitivity to androgen-deprivation therapies, and should be differentiated from unrelated primary tumours originating from other organs.

5.4 Biopsy indication

*5.4.1 **Risk assessment before MRI and biopsy***

An elevated risk of significant PCa is established based on one or more of the primary diagnostic tools applied, such as PSA level, other serum biomarker, DRE or primary imaging. While in the classic diagnostic algorithm the indication for biopsy was generally solely based on a PSA threshold or abnormal DRE, different two- or three-tier sequential/conditional pathways are now available to indicate prostate biopsy, such as imaging and/or biomarkers. These can be combined and/or sequenced into two-tier or multitier conditional diagnostic pathways (e.g. PSA -> MRI, PSA -> risk calculator, PSA -> risk calculator -> MRI, and so on). Age, comorbidity, life expectancy and therapeutic consequences should also be considered and discussed beforehand [243].

The chosen diagnostic algorithm can be elected based on availability, expertise and resources. The various approaches impact cancer detection rates, number of (un)necessary biopsies, number of patient visits and option of targeted biopsies. The elected strategy can also be decided based on prevalence of disease in men entering the pathway (e.g. screening versus clinical symptoms).

Different sequences and combinations of these tools lead to different rates of biopsy indications and detection rates of insignificant PCa and significant PCa, but also on the burden and costs of the diagnostic algorithm [367].

For re-evaluation of the initial PSA value and the use of PSA-D in risk assessment before MRI, see Sections 5.2.2 and 5.2.3).

5.4.1.a Risk calculators assessing the risk of csPCa

At different steps during the diagnostic process, available parameters may be combined into risk calculators to optimise risk assessment of csPCa. Validation and adaption to the target population are critical issues before use. Risk calculators which combine clinical data (age, DRE findings, PSA level, prostate volume, etc.) may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby improving the balance of the cancer detection rates and number of biopsies [368].

Several tools developed as a result of cohort studies are available, including (among others) the calculator derived from the ERSPC cohort (http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators) that has been updated by incorporating the 2014 ISUP Pathology Gleason Grading and Cribriform growth [181], and the calculator derived from the Prostate Cancer Prevention Trial (PCPT) cohort (PCPTRC 2.0 http://myprostatecancerrisk.com). However, calculators are limited by their dependency on disease prevalence. All calculators show miscalibration when tested in populations with a different prevalence than that of the training population of the model. Recalibrations taking into account the local prevalence are possible, but this approach is difficult in routine practice, because the local prevalence is difficult to estimate and may change over time. In an SR initiated by the 'Prostate Cancer Awareness and Initiative for Screening in the European Union' (PRAISE-U) group all currently available risk calculators are listed. The SR underscores the need for updates, validation and adaption of risk calculators to accommodate local differences in patient population [215]. Available risk calculators which have been externally validated ≥ 5 times are listed in Table 5.4.

Table 5.4 Available risk calculators assessing the risk of csPCa (externally validated five or more times) [215]

Available risk calculators with ≥ 5 external validations before MRI		
	AUC (aggregated)	**Factors included**
PBCG RC	0.70	PSA, DRE, Age, PBx, FH, BMI
RPCRC-RC3/4	0.75	PSA, DRE, PBx, PV
RPCRC-RC3	0.78	PSA, DRE, PBx, PV
PCPTRC 2.0	0.69	PSA, DRE, Age, PBx, FH, BMI
RPCRC-RC3/4-DRE	0.74	PSA, DRE, PBx, PV
PCPTRC	0.70	PSA, DRE, Age, PBx, FH, BMI
Including blood biomarker		

4Kscore Test	0.82	tPSA, fPSA, iPSA, hK2, PSA, DRE, Age, PBx
Stockholm3 model	0.80	fPSA, GDG15, PSP94, fhK2, 101 SNPs, PSA, DRE, Age, PBx, PV, FH
After MRI		
MRI-RPCRC-RC3/4	0.82	PSA, DRE, PBx, PV, TRUS, PIRADS
Van Leeuwen	0.86	PSA, DRE, PBx, PV, PI-RADS
Radtke	0.83	PSA, DRE, Age, PV, PI-RADS
Mehralivand	0.82	DRE, Age, PBx, PV, Race, PSA-D, PI-RADS

BMI = body mass index; DRE = digital rectal exam; FH = family history; fPSA = free PSA; iPSA = initial PS; PBx = prior biopsy; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate specific antigen; PSA-D = PSA density; PV = prostate volume; tPSA = total PSA; TRUS = transrectal ultrasound.

5.4.1.b Using risk stratification to avoid magnetic resonance imaging scans and biopsy procedures

Use repeated PSA if the initial PSA is between 3 and 10ng/mL and use PSA-D in risk stratification (see Sections 5.2.2 and 5.2.3).

A retrospective analysis including 200 men from a prospective database of patients who underwent MRI and combined systematic and targeted biopsy showed that upfront use of the Rotterdam Prostate Cancer Risk Calculator would have avoided MRI and biopsy in 73 men (37%). Of these 73 men, ten had ISUP GG 1 cancer and four had ISUP GG ≥ 2 cancer [369]. A prospective multicentre study evaluated several diagnostic pathways in 545 biopsy-naïve men who underwent MRI and systematic and targeted biopsy. Using a PHI threshold of > 30 to perform MRI and biopsy would have avoided MRI and biopsy in 25% of men, at the cost of missing 8% of the ISUP GG ≥ 2 cancers [370]. Another prospective multicentre trial including 532 men (with or without history of prostate biopsy) showed that using a threshold of ≥ 10% for the Stockholm3 test to perform MRI and biopsy would have avoided MRI and biopsy in 38% of men, at the cost of missing 8% of ISUP GG ≥ 2 cancers [286]. Finally, a risk calculator developed on 1,486 men who underwent MRI and biopsy was externally validated on a cohort of 946 men from two institutions. Using a risk threshold that provided 95% sensitivity in the development cohort could have avoided 22% of the MRI scans in the validation cohort while missing 5% of csPCa [371].

In conclusion, as long as patients with a low risk score on the risk calculator are offered repeat testing and follow-up until they have a life expectancy of < 15 years, it seems unlikely that any preliminary missed case would cause increased morbidity or lead to PCSM.

*5.4.2 **MRI-based indication for biopsy***

5.4.2.a MRI as a triage test for biopsy ('MRI pathway')

Owing to its high sensitivity, MRI showed an excellent NPV for ruling out the presence of csPCa, not only at subsequent biopsy [372], but also after four years of follow-up [373, 374].

The diagnostic yield and number of biopsy procedures potentially avoided by MRI triage depends on the Likert/PI-RADS threshold used to define a positive MRI. In a meta-analysis on PI-RADS v2.1 data [229], PI-RADS ≥ 3 thresholding showed MRI sensitivity/specificity for significant disease of 96%/43% on a patient level for ISUP GG ≥ 2 cancer (15 reports, 4,484 men), while PI-RADS ≥ 4 thresholding showed sensitivity/specificity of 88%/64% (21 reports, 5,745 men). On a patient level, the distribution of PI-RADS categories was PI-RADS 1: 9%, PI-RADS 2: 29%, PI-RADS 3: 19%, PI-RADS 4: 22%, and PI-RADS 5: 19%, suggesting a potential biopsy reduction of 38% when thresholding at PI-RADS ≥ 3.

In pooled studies on biopsy-naïve patients and patients with prior negative biopsies, a Likert/PI-RADS threshold of ≥ 3 would have avoided 30% (95% CI: 23-38) of all biopsy procedures while missing 11% (95% CI: 6-18) of all detected ISUP GG ≥ 2 cancers (relative percentage) [226]. Increasing the threshold to ≥ 4 would have avoided 59% (95% CI: 43-78) of all biopsy procedures while missing 28% (95% CI: 14-48) of all detected ISUP GG ≥ 2 cancers [226]. Of note, the percentages of negative MRI (Likert/PI-RADS score ≤ 2) may show substantial variability among series (between 21-49%) [135, 264, 375].

In the MR PROPER trial - a prospective, multicentre, non-randomised opportunistic early detection setting (PSA > 3ng/mL) - comparable rates of ISUP GG ≥ 2 cancer detection (24% vs. 25%) were obtained by the MRI pathway and by a strategy indicating systematic biopsy based on a risk calculator [376]. However, the MRI pathway avoided biopsy in more men as compared to the diagnostic pathway using a risk calculator (559/1015, 55% vs. 403/950, 42%; difference -13%, 95% 27 CI: -17% to -8.3%; p < 0.01). It also detected fewer ISUP GG

1 cancers (84/1015, 8.3% vs. 121/950, 13%; difference 4.5%, 95% CI: 1.8-7.2%; p < 0.01) [376]. As a result of testing lower-risk men in current practice (i.e., opportunistic setting), a higher rate of prostate biopsies can be avoided by MRI triage.

5.4.2.b Combining MRI and PSA Density

Prostate-specific antigen density (PSA-D) may help refine the risk of csPCa in patients undergoing MRI as PSA-D and the PI-RADS score are significant independent predictors of csPCa at biopsy [377, 378]. Combinations of PSA-D and MRI have been explored [230, 379], showing guidance in biopsy decisions whilst safely avoiding redundant biopsy testing and detection of insignificant PCa. In a meta-analysis of eight studies, pooled MRI NPV for ISUP GG ≥ 2 cancer was 84% (95% CI: 81-87) in the entire cohort, 83% (95% CI: 80-84) in biopsy-naïve men and 88% (95% CI: 85-91) in men with prior negative biopsies. In the subgroup of patients with PSA-D < 0.15ng/mL/cc, NPV increased to 90% (95% CI: 87-93), 89% (95% CI: 83-93) and 94% (95% CI: 91-97), respectively [380]. In contrast, the risk of ISUP GG ≥ 2 cancer is as high as 27-40% in patients with negative MRI and PSA-D > 0.15-0.20ng/mL/cc [375, 378, 379, 381-383].

Based on a meta-analysis of > 3,000 biopsy-naïve men, a risk-adapted data table of csPCa was developed, linking PI-RADS score (1-2, 3, and 4-5) to PSA-D categories (< 0.10, 0.10-0.15, 0.15-0.20 and > 0.20ng/mL) (Table 5.5) [230]. This risk-adapted matrix table may guide the decision to perform a biopsy. The safety of this risk-based biopsy guidance was confirmed by a cohort study of 2,055 biopsy-naïve men [384].

In a multicentre retrospective cohort of 1,476 men with PIRADS 3 lesions and a prevalence of 18.5% of ISUP GG ≥ 2 cancer, age, prior negative biopsy and PSA-D were significant independent predictors of the presence of ISUP GG ≥ 2 cancer at subsequent systematic and targeted biopsy. Applying a PSA-D cut-off of 0.15ng/mL/cc, 817 biopsy procedures (58.4%) would have been avoided, at the cost of missing ISUP GG ≥ 2 cancer in 91 men (6.5%), while ISUP GG 1 cancer would not have been detected in 115 men (8.2%) [385]. Two studies provided follow-up data for patients with PI-RADS scores of 1-3 and PSA-D < 0.15ng/ml/cc for whom biopsy was omitted. The cumulative incidence of ISUP GG ≥ 2 cancer detection was 1.3% at two years [386] and 3.2% at 36 months [387].

Table 5.5: Risk data table of clinically significant prostate cancer related to PI-RADS score and PSA D categories in biopsy-naïve men clinically suspected of having significant disease [230]*

Detection of clinically significant prostate cancer (ISUP GG 2 and higher)					
		PSA-density risk groups			
PI-RADS risk categories	Prevalence ISUP GG ≥ 2 PCa	Low < 0.10	Intermediate-low 0.10-015	Intermediate-high 0.15-0.20	High ≥ 0.20
		31% (678/2199)	28% (612/2199)	16% (360/2199)	25% (553/2199)
Compiled totals of csPCa risk					
PI-RADS 1-2	6% (48/839)	3% (11/411)	7% (17/256)	8% (8/104)	18% (12/68)
PI-RADS 3	16% (41/254)	4% (3/74)	13% (11/88)	29% (12/41)	29% (15/51)
PI-RADS 4-5	62% (687/1106)	31% (59/189)	54% (144/286)	69% (148/215)	77% (336/434)
All PI-RADS	35% (776/2199)	11% (73/674)	28% (172/612)	47% (168/360)	66% (363/553)
Risk-adapted matrix table for biopsy decision management					
PI-RADS 1-2		No biopsy	No biopsy	No biopsy	Consider biopsy
PI-RADS 3		No biopsy	Consider biopsy	Strongly consider biopsy	Perform biopsy
PI-RADS 4-5		Perform biopsy	Perform biopsy	Perform biopsy	Perform biopsy

Very low	0-5% csPCa (below population risk) [194].
Low	5-10% csPCa (acceptable risk)
Intermediate-low	10-20% csPCa
Intermediate-high	20-30% csPCa
High	30-40% csPCa
Very high	> 40% csPCa

**Table adapted from: Schoots, IG and Padhani AR. BJU Int 2021 127(2):175. Risk-adapted biopsy decision based on prostate magnetic resonance imaging and prostate-specific antigen density for enhanced biopsy avoidance in first prostate cancer diagnostic evaluation, with permission from Wiley.*

5.4.2.c Risk calculators incorporating MRI findings

Several groups have developed comprehensive risk calculators that combine MRI findings with simple clinical data as a tool to predict subsequent biopsy results [388]. Some calculators underwent external validation with good results both in terms of discrimination and clinical utility and tended to outperform risk calculators not incorporating MRI findings [389-393]. However, their use is hindered by their miscalibration due to prevalence dependency (see Section 5.4.1.a).

5.4.2.d MRI in population-based screening protocols

MRI as a sequential screening tool following PSA

A meta-analysis comparing the use of PSA followed by MRI (sequential) with PSA-only screening methods in terms of clinically significant CDR did not show any significant difference when thresholding at PI-RADS ≥ 3 (OR: 1.02 [0.75-1.37]; p = 0.86) [173]. However, the MRI pathway was associated with lower odds of insignificant PCa detection (OR: 0.34 [0.23-0.49]; p = 0.002). Moreover, MRI and MRI-sequential screening methods had a higher PPV for detecting significant PCa (OR: 4.15 [2.93-5.88]; p = 0.001) and a lower biopsy rate (OR: 0.28 [0.22-0.36]; p < 0.001) than PSA-only-based methods. Thresholding at PI-RADS ≥ 4 showed even lower odds of insignificant PCa detection (OR: 0.23; 95% CI: 0.05-0.97; p = 0.048) and biopsy (OR: 0.19; 95% CI: 0.09-0.38; p = 0.01), with a higher PPV (OR: 7.01; 95% CI: 1.76-27.98; p = 0.03) and similar clinically significant CDR (OR: 0.85; 95% CI: 0.49-1.45; p = 0.23) compared with standard PSA-only screening [173].

For second-stage MRI, the frequency of indeterminate MRI results (MRI score 3) was observed in approximately 20% of second-stage MRI screening interpretations (range 8-43%); and the frequency of scores of 1 or 2 was approximately 60% (e.g. OPT 59%; STHLM3-MRI 56%; Göteborg-2 control arm 59%; and Göteborg-2 experimental arm 61%) [395-398]. Therefore, in a population-based screening setting, the 'MRI pathway' may reduce the risk of overdiagnosis by two thirds, without substantially compromising clinically significant tumours. However, these results were obtained at single academic centres with double reading of the MRI, which may limit their generalisability in less experienced centres (see Section 5.5.5).

MRI as a first-line screening tool

Studies have suggested a role for MRI as a first-line screening tool with the aim of detecting csPCa even at PSA levels below the commonly adopted thresholds. However, the frequency of negative MRI results is higher in first-line MRI screening compared to second-line triage (range, 66-89%) [399-403]. Thresholding at a PI-RADS ≥ 4 in MRI as the primary screening tool, clinically significant and insignificant CDRs were 6% [0.6-39%] and 1.2% [0.2-7%], respectively [399, 404, 405]. The PPV of upfront MRI to detect significant PCa was 42% [16-73%].

The GG ≥ 2 cancer detection rates in MRI-positive men undergoing targeted and systematic biopsies were generally higher in second-stage MRI screening than in first-line MRI screening (range, 31-62% vs. 22-27%), likely due to the higher disease prevalence due to PSA preselection [395]. The wide variation in GG ≥ 2 cancer detection rates across studies cannot be explained solely by differences in MRI utilisation and MRI-targeted biopsy approaches. Age differences in study inclusion and differences in PSA positivity also contributed by affecting the GG ≥ 2 cancer prevalence.

5.4.3 Micro-US-based indication for biopsy

High-resolution micro-US-guided biopsy can complement MRI fusion-guided biopsy for PCA diagnosis. The OPTIMUM trial, a multicentre, international, open-label, randomised, non-inferiority trial of biopsy-naïve patients, compared micro-US-guided and MRI fusion-guided biopsy in patients with clinical suspicion of PCa (elevated PSA and/or abnormal DRE findings) [270]. Patients were randomised in a 1:2:3 ratio to undergo micro-US-guided biopsy without MRI (micro-US), combined MRI/micro-US fusion-guided biopsy (micro-US/MRI), or software-assisted MRI/conventional US fusion-guided biopsy (MRI/conUS). The primary outcome was the difference in detection of GG 2 or higher cancers using micro-US-guided plus systematic biopsy versus MRI/conUS-guided plus systematic biopsy.

Grade group 2 or higher cancer was detected in 57 participants (47%) in the microUS group, in 141 (43%) in the MRI/conUS group, and in 106 (47%) in the micro-US/MRI group. Micro-US-guided biopsy was non-inferior to MRI fusion-guided biopsy (difference, 3.5% [95% CI: −3.95% - 10.92%]; non-inferiority p < .001; non-inferiority margin set at 10%). Combined biopsy with micro-US/MRI was also non-inferior to MRI/conUS-guided biopsy (difference, 4.3% [95% CI: −4.06% to 12.63%]; non-inferiority p < .001). Grade group 2 or higher cancer diagnosed by targeted biopsy only was 38% in the micro-US group, 34% in the MRI/conUS group, and 40% in the micro-US/MRI group; these differences were not significant. Of note, 20% of the patients who had micro-US had negative findings (PIRIMUS 1-2), while 32% of patients who underwent MRI had negative findings (PI-RADS 1-2) suggesting that the micro-US pathway could avoid less biopsies than the MRI pathway [270]. Another prospective trial found similar results [267].

5.5 Biopsy strategy

Prostate biopsy can be performed using various strategies (systematic, targeted, etc.) and approaches (i.e. transperineal versus transrectal).

*5.5.1 **Systematic biopsy strategy***

For systematic biopsies in which no prior imaging is used for targeting, the sample sites should be bilateral from apex to base, as far posterior and lateral as possible in the peripheral gland, regardless of the approach used. A 2006 SR showed that 12 is the minimum number of cores for systematic biopsies, with > 12 cores not increasing cancer detection rate significantly [406].

*5.5.2 **Targeted biopsy strategy***

Where MRI has shown a suspicious lesion, MR-targeted biopsy can be obtained through cognitive guidance, US/MR fusion software or direct in-bore guidance. Current literature, including SRs and meta-analyses, does not show a clear superiority of one image-guided technique over another [407-409]. The Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies (FUTURE) randomised trial compared three techniques (cognitive fusion, software fusion and in-bore MRI) of MRI-targeted biopsy in the repeat-biopsy setting and found no differences in cancer detection [408]. However, it was underpowered for this conclusion.

*5.5.3 **Targeted biopsy versus systematic biopsy***

5.5.3.a Increased detection of cancers labelled as clinically significant

The PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) [135] and PRECISE (Prostate Evaluation for Clinically Important Disease: MRI vs. Standard Evaluation Procedures) [410] prospective trials randomised biopsy-naïve patients to either ten- to twelve-core systematic biopsy or to MRI with subsequent MRI-targeted biopsy (up to four cores) in case of positive MRI. These trials found that MRI-targeted biopsy significantly outperformed [135] or was not inferior to [410] systematic biopsy for the detection of ISUP GG ≥ 2 cancers. In pooled data of 25 reports on agreement analysis (head-to-head comparisons) between systematic biopsy (median number of cores: 8-15) and MRI-targeted biopsies (median number of cores: 2-7), the detection ratio (i.e. the ratio of the detection rates obtained by MRI-targeted biopsy alone and by systematic biopsy alone) was 1.12 (95% CI: 1.02-1.23) for ISUP GG ≥ 2 cancers and 1.20 (95% CI: 1.06-1.36) for ISUP GG ≥ 3 cancers, and therefore in favour of MRI-targeted biopsy [168]. Another meta-analysis of studies limited to biopsy-naïve patients with a positive MRI also found that MRI-targeted biopsy detected significantly more ISUP GG ≥ 2 cancers than systematic biopsy (risk difference, -0.11 [95% CI: -0.2-0.0]; p = 0.05) [411]. This data was further confirmed in another prospective multicentre trial [412].

In a subgroup of 152 patients from the FUTURE trial who underwent both MRI-targeted biopsy and systematic biopsy in a repeat biopsy setting, MRI-targeted biopsy detected significantly more ISUP GG ≥ 2 cancers than systematic biopsy (34% vs. 16%; p < 0.001, detection ratio of 2.1) [413]. These findings support the claim that MRI-targeted biopsy significantly outperforms systematic biopsy for the detection of ISUP GG ≥ 2, including in the repeat-biopsy setting.

5.5.3.b Reduced detection of cancers labelled ISUP GG 1

In pooled data of 25 head-to-head comparisons between systematic biopsy and MRI-targeted biopsy, the detection ratio for ISUP GG 1 cancers was 0.62 (95% CI: 0.44-0.88) in patients with prior negative biopsy and 0.63 (95% CI: 0.54-0.74) in biopsy-naïve patients [226]. In the PRECISION and 4M trials, the detection rate of ISUP GG 1 patients was significantly lower in the MRI-targeted biopsy group as compared to systematic biopsy (9% vs. 22%, p < 0.001, detection ratio of 0.41 for PRECISION; 14% vs. 25%, p < 0.001, detection ratio of 0.56 for 4M) [135, 375]. In the MRI-FIRST trial, MRI-targeted biopsy detected significantly fewer patients with clinically insignificant PCa (defined as ISUP GG 1 and maximum cancer core length < 6 mm) than systematic biopsy

(5.6% vs. 19.5%, p < 0.0001, detection ratio of 0.29) [264]. Consequently, MRI-targeted biopsy without systematic biopsy significantly reduces overdiagnosis of low-risk disease compared to systematic biopsy. This seems true even when systematic biopsies are indicated after risk stratification with the Rotterdam Prostate Cancer Risk Calculator) [376].

5.5.3.c Added value of systematic biopsy and targeted biopsy

From head-to-head comparisons between the two biopsy techniques, it is possible to compute their added value, i.e. the percentage of additional patients with csPCa they help diagnose. Table 5.6 shows the added value of systematic and MRI-targeted biopsy for ISUP GG ≥ 2 and ≥ 3 cancer detection. The absolute added values in the table refer to the percentage of patients in the entire cohort. If the cancer prevalence is considered, the 'relative' percentage of additional detected csPCa can be calculated. Adding MRI-targeted biopsy to systematic biopsy in biopsy-naïve patients increases the number of detected ISUP grade ≥ 2 and grade ≥ 3 PCa by approximately 20% and 30%, respectively. In the repeat-biopsy setting, adding MRI-targeted biopsy increases detection of ISUP GG ≥ 2 and GG ≥ 3 PCa by approximately 40% and 50%, respectively. Omitting systematic biopsy in biopsy-naïve patients would miss approximately 16% of all detected ISUP GG ≥ 2 PCa and 18% of all ISUP grade ≥ 3 PCa. In the repeat-biopsy setting, it would miss approximately 10% of ISUP GG ≥ 2 PCa and 9% of ISUP GG ≥ 3 PCa. The low added value of systematic biopsy in the repeat biopsy setting has been further confirmed by other studies that reported absolute added values of 1.2-3.9% for the detection of ISUP GG ≥2 cancers and of 1.2-1.6% for ISUP GG ≥ 3 cancers [413-415].

Table 5.6: Absolute added values of targeted and systematic biopsies for ISUP grade ≥ 2 and ≥ 3 Cancer Detection

		ISUP GG ≥ 2			ISUP GG ≥ 3		
ISUP grade		**Cochrane meta-analysis*** [226]	**MRI-FIRST trial*** [264]	**4M trial** [375]	**Cochrane meta-analysis*** [226]	**MRI-FIRST trial*** [264]	**4M trial** [375]
Biopsy-naïve	Added value of MRI-TBx	6.3% (4.8-8.2)	7.6% (4.6-11.6)	7.0% (ND)	4.7% (3.5-6.3)	6.0% (3.4-9.7)	3.2% (ND)
	Added value of systematic biopsy	4.3% (2.6-6.9)	5.2% (2.8-8.7)	5.0% (ND)	2.8% (1.7-4.8)	1.2% (0.2-3.5)	4.1% (ND)
	Overall prevalence	27.7% (23.7-32.6)	37.5% (31.4-43.8)	30% (ND)	15.5% (12.6-19.5)	21.1% (16.2-26.7)	15% (ND)
Prior negative biopsy	Added value of MRI-TBx	9.6% (7.7-11.8)	-	-	6.3% (5.2-7.7)	-	-
	Added value of systematic biopsy	2.3% (1.2-4.5)	-	-	1.1% (0.5-2.6)	-	-
	Overall prevalence	22.8% (20.0-26.2)	-	-	12.6% (10.5-15.6)	-	-

**Intervals in parenthesis are 95% CI. The absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique.*
ISUP = International Society of Urological Pathology (grade); MRI-TBx = magnetic resonance imaging-targeted biopsies; ND = not defined.

Table 5.7: Detection rates of ISUP GG 1 cancers by targeted and systematic biopsies

Study	Targeted biopsy	Systematic biopsy	p-value
PRECISION [135]	9%	22%	<0.001
PRECISE [410]	10.1	21.7	<0.001
MRI-FIRST [264]*	5.6%	19.5%	<0.0001
4M [375]	14%	24.7%	<0.0001
Cochrane meta-analysis [226]	13.5%	22.4%	<0.01

** In the MRI-FIRST trial, the percentages refer to the detection rates of ISUP GG 1 cancers with a maximum cancer core length < 6 mm.*

*5.5.4 **Perilesional biopsy***

A minimum of three to five cores is required for proper sampling of an MRI-detected lesion [237, 415, 416]. Several concordant studies showed that, in case of a unilateral MRI lesion, contralateral systematic biopsy (i.e., from the MRI-negative lobe) has little added value for diagnosing csPCa (0.3-4%). Paradoxically, the added value of ipsilateral systematic biopsy is higher (4.9-18.4%) and comes mostly from the systematic cores obtained in the sextant containing the MR lesion, or the sextant immediately adjacent [417-421]. Consequently, including additional perilesional/regional systematic biopsies, rather than standard sextant-based systematic biopsies may decrease the total number of cores taken (by avoiding systematic biopsies in MRI-negative lobes) and improve the detection of csPCa (by compensating for guiding imprecision). In addition, the MRI-targeted and regional biopsy approach could avoid detecting 12-17% of the insignificant cancers detected by the classical combined approach [422-424].

A meta-analysis of eight studies showed a non-significant difference in detection of ISUP GG ≥ 2 cancer in the MRI-directed, targeted and regional biopsy approach, compared to the recommended practice of MRI-directed targeted and systematic biopsy approach (RR: 0.95, 95% CI: 0.90–1.01; p = 0.09). However, the MRI-directed targeted and regional biopsy approach detected significantly more ISUP GG ≥ 2 cancers than MRI-targeted biopsy alone (RR: 1.18, 95% CI: 1.10–1.25; p < 0.001) [425].

A meta-analysis of 21 studies also supported the targeted and regional biopsy approach as a valuable strategy for the detection of ISUP GG ≥ 2 cancer in MRI-visible lesions while avoiding overdiagnosis of ISUP GG 1 cancer [426]. The overall GG ≥ 2 cancer detection yield of the reference group was 46% and 44% in the targeted and regional biopsy approach (OR: 1.07, 95% CI: 0.99–1.16, p = 0.07). A further subgroup analysis of targeted and ipsilateral biopsies (excluding perilesional biopsies) did not show significant differences in GG ≥ 2 cancer detection (OR: 1.09, 95% CI: 0.98–1.21, p = 0.13). The targeted and regional biopsy approach significantly avoided overdiagnosis of ISUP GG 1 cancer (OR: 1.16, 95% CI: 1.04–1.30, p = 0.008) [426]. However, some aspects still need to be addressed, including standardisation of the number and spatial placements of targeted and perilesional biopsies, its value in equivocal cases (PI-RADS 3 category) as well as the area defining the perilesional zone in relation to the size of the MRI target.

*5.5.5 **MRI-targeted biopsy reproducibility***

The accuracy of MRI-targeted biopsy is also substantially impacted by the experience of the biopsy operator [237]. The PRECISE trial, which reproduced the design of the PRECISION trial, obtained quite different results. In both trials, the detection rate for ISUP GG ≥2 PCa was higher for the MRI pathway than for the classical systematic biopsy pathway. Yet, the difference was much lower in the PRECISE trial (+5.2% vs. +12.1% for ISUP GG ≥ 2 cancers; +2.1% vs. +5.5% for ISUP GG ≥ 3 cancers). In addition, there was major intersite variability in the PRECISE trial: the centre with the highest csPCa detection rate on MRI-targeted biopsy had the lowest csPCa detection rate on systematic biopsy and vice versa [410].

These factors of variability give rise to concerns regarding the reproducibility of the satisfactory results of the MRI-directed diagnostic pathways. Efforts towards standardisation of the entire diagnostic pathway (MRI acquisition and interpretation, biopsy planning and acquisition) through quality assurance and quality control are currently undertaken [237, 427]. However, significant improvement in the accuracy of MRI and MRI-targeted biopsy can be observed over time through simple measures such as training and participation to MDT meeting with pathological correlation and feedback [237, 428].

*5.5.6 **MRI-targeted biopsy in younger men (45-55 years)***

A *post-hoc* analysis on the German PROBASE screening trial, suggests that for men between 45 and 55 years, systematic biopsies remain a critical component for cancer detection [177]. While MRI identified 91% (135/148) of all GG ≥ 2 cancers, only 74% (109/148) were detected by transrectal MRI-targeted biopsies. In contrast, 94% (139/148) GG ≥ 2 cancers were detected by concomitant transrectal systematic biopsies. This targeting failure was explained by unfavourable tumour location and small tumours. In terms of tumour location, discrepancies for anterior, apical, and lateral lesions were observed, which are often more difficult to reach via transrectal than transperineal access. Targeting failures for small tumours could potentially be reduced by the perilesional biopsy approach which was not performed during the study. Furthermore, smaller prostate volumes in younger men allow more effective systematic sampling, increasing the yield of the systematic biopsy approach.

MRI did not identify all GG ≥ 2 cancers (91%). A considerable proportion of examinations had PI-RADS 3 findings (46%; 242/525). Owing to the often diffuse signal changes in the T2- and diffusion-weighted imaging with widespread perfusion enhancement in the peripheral zone, cancer detection on MRI is more challenging in younger men [429]. The lack of standardised acquisition and interpretation protocols during the long inclusion

period, together with the absence of MRI quality assurance between participating centres, may also have contributed to the high PI-RADS 3 results, rather than the reading challenges in younger men.

5.5.7 Cancer grade shift

MRI findings are significant predictors of adverse pathology features on prostatectomy specimens, and of survival-free BCR after RP or RT [113, 430, 431]. In addition, tumours visible on MRI are enriched in molecular hallmarks of aggressivity as compared to invisible lesions [231]. MRI, therefore, does in fact identify aggressive tumours.

Nonetheless, because MRI-targeted biopsy is more sensitive than systematic biopsy in detecting areas of high-grade cancer, the prognosis of all risk groups based on the ISUP GG detected by MRI-targeted biopsy is improved as a result of the Will Rogers phenomenon [113]. This grade shift is further aggravated when only the ISUP GG of the most pejorative biopsy core is taken into consideration. Preliminary findings suggest that, when the grade is different between systematic biopsy and MRI-targeted biopsy [432] or between systematic biopsy and prostatectomy specimens [433], the prognosis is intermediate between grades. This is in line with the 2019 ISUP consensus conference which recommended using an aggregated ISUP GG summarising the results of all biopsy cores from the same MR lesion, rather than using the result from the core with the highest ISUP GG [118] (see Section 4.2).

Table 5.8: Detection rates for ISUP GG ≥ 2 prostate cancer achieved by targeted biopsy, combined systematic and targeted biopsy and targeted biopsy with perilesional sampling

Study	Type of study	N	Targeted biopsy with perilesional sampling vs. Combined systematic and targeted biopsy		Targeted biopsy with perilesional sampling vs. Targeted biopsy	
			Ratio of detection rates	Median number of cores	Ratio of detection rates	Median number of cores
Hagens MJ [425]	Meta-analysis	2,603	0.95 (0.90 - 1.01), p = 0.09	9.5 [7.5-12.3] vs. 16.5 15.3 - 12.3]	1.18 (1.1 - 1.25), p < 0.001	9.5 [7.5 - 12.3] vs. 3.5 [3 - 4]
Hagens MJ [424]	Retrospective, single centre	235	0.968 (0.91 - 0.993)	7 [6 - 9] vs. 12 [10 - 15]	-	-
Hsieh PF [434]	Prospective, single centre	100	1	15 [12.8 - 18] vs. 26 [23 - 28]	1.20, p = 0.008	15 [12.8 - 18] vs. 6 [4 - 7]

**Intervals in parenthesis are 95% CI. Intervals in brackets are interquartile ranges.*

5.5.8 Recommendations for MRI imaging in biopsy indication and strategy

Recommendations	Strength rating
Do not use magnetic resonance imaging (MRI) as an initial screening tool.	Strong
Adhere to PI-RADS guidelines for MRI acquisition and interpretation and evaluate MRI results in multidisciplinary meetings with pathological feedback.	Strong
Where MRI has shown a suspicious lesion, MR-targeted biopsy can be obtained through cognitive guidance, ultrasound/MR fusion software or direct in-bore guidance.	Weak
Perform MRI before prostate biopsy in male patients with suspected organ-confined disease.	Strong
Perform limited biopsy only, without MRI, in males with clear evidence of locally advanced disease on digital rectal examination or those not for curative treatment.	Weak
Combine targeted biopsy with perilesional sampling when MRI is positive (i.e. PI-RADS ≥ 4).	Weak
Omit biopsy and offer PSA monitoring when MRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of PCa is low (PSA density < 0.20 ng/mL/cc and no family history).	Weak
When MRI is indeterminate (PI-RADS = 3), and clinical suspicion of PCa is very low (PSA density < 0.10 ng/mL/cc and no family history), omit biopsy and offer PSA monitoring. Otherwise, consider targeted biopsy with perilesional sampling.	Weak

5.6 Biopsy approach

MRI-directed US-guided prostate biopsy is now the standard of care, although MRI in-bore biopsy is offered in a few centres. MRI-directed US-guided prostate biopsy can be performed using either the transperineal or the transrectal approach. Both can be performed under local anaesthesia [435]. A meta-analysis of nine RCTs including 2,230 patients found that extended biopsy templates (20 vs. 8) showed comparable infectious complications to standard templates (RR: 95% CI: 0.80 [0.53–1.22]) [436]. Additional meta-analyses found no difference in infectious complications regarding needle guide type (disposable vs. reusable), needle type (coaxial vs. noncoaxial), needle size (large vs. small) and number of injections for periprostatic nerve block (standard vs. extended) [436].

5.6.1 MRI-directed transrectal vs transperineal US-guided biopsy

A systematic review and meta-analysis comparing MRI-targeted transrectal (TR) biopsy to MRI-targeted transperineal (TP) biopsy, including eight studies, showed a higher sensitivity for detection of csPCa when the transperineal approach was used (86% vs. 73%) [437]. However, in two subsequent RCTs, csPCa detection was not superior for the TP route compared to TR biopsy [438, 439]. The PREVENT trial showed similar csPCa detection for TP (53%) and TR (50%) routes, while the PERFECT trial showed non-inferior csPCa rates for TP (47%) and TR (54%) [438]. Clinically significant PCa detection was different for anterior and posterior tumours [437, 440]. The PERFECT trial showed higher significant cancer detection rates for anterior tumours with the TP approach (41% in TP and 27% in TR), while the TR approach favoured posterior tumours (44% in TP and 59% in TR) [440]. These findings were further underlined by pooling the data of prospective trials in a meta-analysis with similar detection rates for PCa, infection, urinary retention and managing pain [441].

The TRANSLATE RCT was designed and powered for detecting a difference in csPCa (ISUP GG ≥ 2) between MRI-guided TP and TR biopsies [442]. In 1,126 men randomised in the study, csPCa rates were 60% in TP and 54% in TR arms (OR 1.32 [95% CI 1.03–1.70]; p=0.031), with less severe adverse events observed in the TP arm. This supports TP as a preferred method over TR in csPCa detection at MRI-guided prostate biopsies.

5.6.2 Local anaesthesia prior to biopsy

Ultrasound-guided periprostatic block is recommended [443]. Intrarectal instillation of local anaesthetic cream is inferior to periprostatic infiltration by injection [444]. Local anaesthesia can also be used effectively for MRI-targeted and systematic transperineal biopsy [445]. Patients are placed in the lithotomy position. Approximately 20mL of lignocaine or bupivacaine with or without adrenaline (1 in 200,000) is injected into the perineal skin and subcutaneous tissues anterior to the anus, followed by a periprostatic block also via transperineal route. A SR evaluating pain in three studies comparing transperineal versus transrectal biopsies found that the transperineal approach significantly increased patient pain (RR: 1.83 [1.27–2.65]) [446]. In a randomised comparison, a combination of periprostatic and pudendal block anaesthesia reduced pain during transperineal biopsies compared to periprostatic anaesthesia only [447]. A novel perineal nerve block was shown in an RCT to be superior for the relief of pain during transperineal biopsy procedure vs. conventional periprostatic block (2.80 vs. 3.98; on 1-10 scale) [448]. Targeted biopsies can then be taken by means of a brachytherapy grid or a freehand needle-guiding device under local infiltration anaesthesia [445, 449]. An updated meta-analysis of 28 RCTs with 4,027 patients found no evidence that the use of periprostatic injection of local anaesthesia resulted in more infectious complications than no injection (RR: 95% CI: 1.08 [0.79–1.48]) [436, 450, 451].

5.6.3 Infection rate after transperineal and transrectal prostate biopsy

A total of eight randomised studies including 1,596 patients compared the impact of the biopsy route on infectious complications. Infectious complications were significantly higher following transrectal biopsy (48 events among 789 men) compared to transperineal biopsy (22 events among 807 men) (RR: 95% CI: 2.48 [1.47–4.2]) [436, 450]. In addition, a SR including 165 studies with 162,577 patients described sepsis rates of 0.1% and 0.9% for transperineal and transrectal biopsies, respectively [452]. Finally, a population-based study from the United Kingdom (n = 73,630) showed lower readmission rates for sepsis in patients who had transperineal versus transrectal biopsies (1.0% vs. 1.4%, respectively) [453]. However, two subsequent RCTs comparing infectious complications after TP and TR biopsies did not show significant differences in infection rates. The PREVENT trial compared TP without antibiotic prophylaxis with TR biopsy using rectal culture and targeted antibiotic prophylaxis, and showed that infection rates were 0% in TP and 1.4% in TR (p = 0.059) [438]. In the ProBE-PC trial, TP without routine antibiotic was compared with TR with antibiotic prophylaxis and composite infection rates were 2.7% and 2.6%, respectively [439].

An SR and meta-analysis of eight non-RCTs reported no significant differences between patients receiving or not receiving antibiotic prophylaxis before transperineal biopsy in terms of post-biopsy infection (0.11% vs. 0.31%) and sepsis (0.13% vs. 0.09%) [454]. This is in line with another systematic review and meta-analysis of 112

individual patient cohorts, which also showed no significant difference in the number of patients experiencing post-transperineal-biopsy infection, 1.35% of 29,880 patients receiving antibiotic prophylaxis, and 1.22% of 4,772 men not receiving antibiotic prophylaxis (p = 0.8) [455]. In addition, two RCTs have reported comparably low post-biopsy infection rates for transperineal biopsy regardless of whether antibiotic prophylaxis was administered or not [456, 457]. An SR and meta-analysis, including 106 unique studies, comparing transperineal biopsy with and without prophylactic antibiotics found no significant differences in UTI or sepsis rates [455]. In addition, another SR and meta-analysis of 23 studies (only two RCTs) including 12,324 patients reported no significant differences between patients receiving or not receiving antibiotic prophylaxis in terms of post-biopsy sepsis (0.16% vs. 0.13%) and hospitalisation due to infectious complications (0.35% vs. 0.29%) for the transperineal approach [458]. Thus, there is a substantial body of evidence to suggest that, for patients without significant risk factors, such as diabetes or history of urinary retention [459], antibiotic prophylaxis may be safely omitted for transperineal biopsy.

An updated meta-analysis of eleven RCTs including 2,237 men showed that the use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications (RR: 0.47 95% CI: [0.36–0.61]) [436, 451, 460]. Single RCTs showed an advantage for rectal povidone-iodine preparation before transrectal biopsy compared to after biopsy [461]. A meta-analysis of four RCTs including 671 men evaluated the use of rectal preparation by enema before transrectal biopsy. No significant advantage was found regarding infectious complications (RR: 95% CI: 0.96 [0.64–1.54]) [436].

A meta-analysis of eleven studies with 1,753 patients showed significantly reduced infections after transrectal prostate biopsy when using antimicrobial prophylaxis as compared to placebo/control (RR: 95% CI: 0.56 [0.40–0.77]) [462].

For transrectal biopsies fluoroquinolones have been traditionally used for antibiotic prophylaxis. Recent years, however, have seen an increase in fluoroquinolone resistance. In addition, the European Commission has implemented stringent regulatory conditions regarding the use of fluoroquinolones, resulting in the suspension of the indication for perioperative antibiotic prophylaxis including prostate biopsy [463].

An SR and meta-analysis on antibiotic prophylaxis for the prevention of infectious complications following prostate biopsy concluded that, in countries in which fluoroquinolones are permitted as antibiotic prophylaxis, a minimum of a full one-day administration, as well as targeted therapy in case of fluoroquinolone resistance, or augmented prophylaxis (combination of two or more different classes of antibiotics) is recommended [462]. In countries in which the use of fluoroquinolones are suspended, cephalosporins or aminoglycosides can be used as individual agents with comparable infectious complications based on meta-analysis of two RCTs [462]. A meta-analysis of three RCTs reported that fosfomycin trometamol was superior to fluoroquinolones (RR: 95% CI: 0.49 [0.27–0.87]) [462], but routine general use should be assessed critically due to the relevant infectious complications reported in nonrandomised studies [464]. Of note, the indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany because the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy. Another possibility is the use of augmented prophylaxis without fluoroquinolones, although no standard combination has been established to date. Finally, targeted prophylaxis based on rectal swap/stool culture is plausible, but no RCTs are available on non-fluoroquinolones. See Figure 5.1 for prostate biopsy workflow to reduce infections complications.

Taking into account the feasibility of TP and TR biopsies under local anaesthesia, comparable csPCa detection rates and the growing importance of antibiotic stewardship, the transperineal biopsy route is preferred over transrectal route despite potential logistical challenges.

5.6.4 Summary of evidence and recommendations for performing prostate biopsy (in line with the EAU Urological Infections Guidelines Panel)

Summary of evidence	LE
A meta-analysis of 13 studies including 4,516 patients showed significantly reduced infectious complications in patients undergoing transperineal biopsy as compared to transrectal biopsy.	1a
One randomised controlled trial showed comparable low rates of infectious complication for transperitoneal biopsy without antibiotics and transrectal biopsy with targeted antibiotic prophylaxis.	1a

One randomised controlled trial showed superior detection of csPCa by transperineal biopsy compared with transrectal biopsy.	1a
A meta-analysis of 23 studies (including two RCTs) with 12,324 patients reported comparable rates of post-biopsy infections in patients undergoing transperineal biopsy irrespective if antibiotic prophylaxis was given or not.	2
A meta-analysis of 12 RCTs including 2,437 men showed that use of a rectal povidone-iodine preparation before transrectal biopsy, in addition to antimicrobial prophylaxis, resulted in a significantly lower rate of infectious complications.	1a
A meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after transrectal biopsy when using antimicrobial prophylaxis as compared to placebo/control.	1a

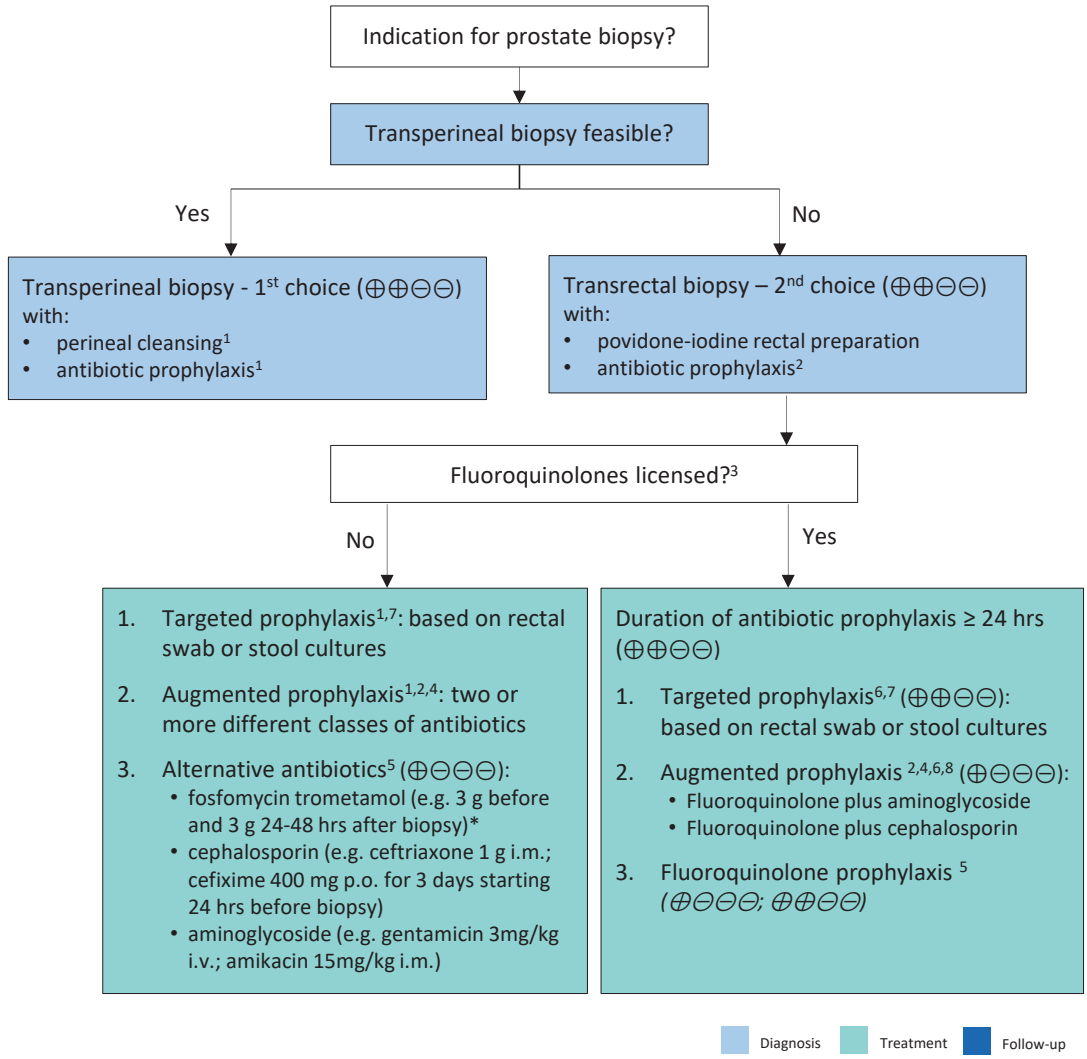
Recommendations	**Strength rating***
Perform prostate biopsy using the transperineal approach due to the low risk of infectious complications and better antibiotic stewardship.	Strong
Omit perioperative antibiotic prophylaxis in transperineal biopsy in patients without risk factors for infectious complications.	Weak
Use routine surgical disinfection of the perineal skin for transperineal biopsy.	Strong
Use rectal cleansing with povidone-iodine prior to transrectal prostate biopsy.	Strong
For antibiotic prophylaxis in transrectal biopsy**, and from an antimicrobial stewardship perspective, the following options are recommended***: • First option: Targeted prophylaxis based on rectal swab or stool culture. • Second option: Augmented prophylaxis (using two or more different classes of antibiotics).	Strong
Ensure that prostate core biopsies from different sites are submitted separately for processing and pathology reporting.	Strong

** The above strength ratings are explained here due to the major clinical implications of these recommendations. Although data showing the lower risk of infection via the transperineal approach is low in certainty, its statistical and clinical significance warrants its strong rating. Strong ratings are also given for routine surgical disinfection of skin in transperineal biopsy and povidone-iodine rectal cleansing in transrectal biopsy because, although the quality of the data is low, the clinical benefit is high and practical application simple. A 'Strong' rating is given for avoiding fluoroquinolones in prostate biopsy due to its legal implications in Europe.*

*** The indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy.*

****While most studies have been performed using fluoroquinolones, the applicability of these findings to non-fluoroquinolone antibiotics remains unclear.*

Figure 5.2: Prostate biopsy workflow to reduce infectious complications*



The following is the suggested workflow for reducing post-biopsy infections.

1. *Multiple systematic reviews including non-RCTs and two RCTs describe comparable rates of post-biopsy infection in patients with and without antibiotic prophylaxis.*
2. *Be informed about local antimicrobial resistance.*
3. *Banned by European Commission due to side effects.*
4. *Contradicts principles of Antimicrobial Stewardship.*
5. *Fosfomycin trometamol (4 RCTs), cephalosporins (2 RCTs), aminoglycosides (2 RCTs).*
6. *Only one RCT comparing targeted and augmented prophylaxis.*
7. *Originally introduced to use alternative antibiotics in case of fluoroquinolone resistance.*
8. *Various schemes: fluoroquinolone plus aminoglycoside (4 RCTs); and fluoroquinolone plus cephalosporin (1 RCT).*

Levels of evidence:

- *High certainty (⊕⊕⊕⊕): very confident that the true effect lies close to that of the estimate of the effect.*
- *Moderate certainty (⊕⊕⊕⊖): moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it will be substantially different.*
- *Low certainty (⊕⊕⊖⊖): confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.*
- *Very low certainty: (⊕⊖⊖⊖) very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.*

This figure has been adapted from Pilatz et al. [462] with permission from Elsevier.
** The indication of fosfomycin trometamol for prostate biopsy has been withdrawn in Germany as the manufacturers did not submit the necessary pharmacokinetic data in support of this indication. Urologists are advised to check their local guidance in relation to the use of fosfomycin trometamol for prostate biopsy.*

5.6.5 Complications

Complications of TRUS biopsy are listed in Table 5.9 [465]. Mortality after prostate biopsy is extremely rare and is usually a consequence of sepsis [466]. Low-dose aspirin is not an absolute contra-indication [467]. An SR found favourable infection rates for transperineal compared to TRUS biopsies with similar rates of haematuria, haematospermia and urinary retention [468]. A meta-analysis of 4,280 men randomised between transperineal versus TRUS biopsies in 13 studies found no significant differences in complication rates. However, data on sepsis compared only 497 men undergoing TRUS biopsy to 474 having transperineal biopsy. The transperineal approach required more local anaesthesia or other type of anaesthesia [469].

Table 5.9: Adverse events of three groups of targeted biopsy [465] *

	Overall (n = 234)	Transrectal MRI-TB (n = 77)	Transperineal FUS-TB (n = 79)	Transrectal COG-TB (n = 78)	p value
Clavien-Dindo grade	-	-	-	-	< 0.001
No adverse events	30.3 (71)	47.4 (36)	29.1 (23)	15.4 (12)	-
Grade 1	63.2 (148)	50.0 (38)	65.8 (52)	74.4 (58)	-
Grade 2	6.0 (14)	2.6 (2)	5.1 (4)	10.3 (8)	-
Grades 3, 4, 5	-	-	-	-	-
Haematuria	53.4 (125)	35.5 (27)	50.6 (40)	74.4 (58)	< 0.001
Haematospermia	37.2 (87)	26.3 (20)	35.4 (28)	50.0 (39)	< 0.01
Rectal bleeding	3.4 (8)	2.6 (2)	2.5 (2)	5.1 (4)	0.59
UTI	3.4 (8)	2.6 (2)	1.3 (1)	6.4 (5)	0.21
Fever	3 (7)	1.3 (1)	2.5 (2)	5.1 (4)	0.46
Urinary retention	3 (7)	-	3.8 (3)	-	0.15
Haematoma	1.3 (3)	-	3.8 (3)	-	0.29
Other	-	-	-	-	0.56
Lower back pain	0.9 (2)	1.3 (1)	1.3 (1)	-	-
Atrial fibrilation	0.4 (1)	-	1.3 (1)	-	-

COG-TB = cognitive registration TRUS targeted biopsy; FUS-TB = MRI-TRUS fusion targeted biopsy; MRI = magnetic resonance imaging; MRI-TB = in-bore MRI targeted biopsy; TB = targeted biopsy; TRUS = transrectal ultrasound; UTI = urinary tract infection. Data are presented as % (n).
**With permission from Elsevier.*

5.7 What diagnostic pathway in clinical practice?

The 'combined pathway', in which patients with a positive MRI undergo combined systematic and targeted biopsy, and patients with a negative MRI undergo systematic biopsy, maximises the detection of ISUP GG ≥ 2 cancers. However, it has the disadvantage of leading to a greater detection of ISUP GG 1 cancers and of referring all patients with a clinical suspicion of cancer to biopsy. Given the growing concerns about overdetection of insignificant PCa, the development of AS protocols in patients with ISUP GG 2 cancers (see Section 6.2.1.b) and the grade shift induced by MRI-targeted biopsy (see Section 5.5.6), the clinical relevance of a diagnostic strategy aimed only at maximising the detection of ISUP GG ≥ 2 cancers, disregarding its negative effects, is questionable [470, 471].

The 'MRI pathway', in which patients with a positive MRI undergo only MRI-targeted biopsy and patients with a negative MRI are not biopsied at all, could avoid biopsy in 21-49% of the patients if a PI-RADS threshold of ≥ 3 is used to trigger biopsy [135, 226, 264, 375], at the cost of missing a small number of mainly ISUP GG 2 cancers, especially in biopsy-naïve patients or in highly selected populations with high prevalence of csPCa (in which the MRI NPV decreases) [372, 472].

Adding perilesional sampling to targeted biopsy could mitigate the drawbacks of the 'MRI pathway' by maintaining good detection of csPCa while decreasing the overdiagnosis of insignificant cancer (see Section 5.5.4). Due to the low NPV of MRI in high-risk populations, systematic biopsies are still necessary in patients with negative MRI and high clinical suspicion of PCa, e.g. high PSA density.

MRI-directed pathways were compared to the classical combined pathway in a retrospective cohort of 499 men. The highest clinical utility above a risk threshold of 6.25% was obtained by means of a risk-based pathway in which patients with a PI-RADS score of 1-3 and a low-risk profile (PSA-D < 0.15ng/ml/cc, negative DRE, no family history, no ASAP or ISUP1 cancer at prior biopsy) could forgo biopsy while the others underwent combined systematic and MRI-targeted biopsy. In this pathway, biopsy could have been avoided in 99 men (19%) while missing ISUP GG ≥ 2 cancers in only six men (1.2%) [473].

*5.7.1 **Repeat biopsy after negative biopsy***

During follow-up after a negative systematic biopsy, the incidence of PCa is higher, but the risk of PCa death is lower than the population average [474]. Men with prior negative systematic biopsy and persistent suspicion of PCa should have an MRI if one has not already been performed.

Significant PCa may still be present in men with abnormal MRI and negative targeted biopsy [475]. Therefore, follow-up or direct repeat biopsy should be considered dependant of risk factors (e.g. PSA density, PI-RADS score).

In a contemporary series of biopsies, the likelihood of finding a csPCa after follow-up biopsy after a diagnosis of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia (PIN) was only 6-8% - not significantly different from follow-up biopsies after a negative biopsy [476, 477]. Therefore, routine re-biopsies in this setting are not required.

The added value of other biomarkers remains unclear (see Section 5.2.7).

*5.7.2 **Saturation biopsy***

The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30–43% and depends on the number of cores sampled during earlier biopsies [478]. Saturation biopsy may be performed using the transperineal technique, which detects an additional 38% of PCa. The rate of urinary retention varies substantially from 1.2% to 10% [323, 479].

However, given the very low risk of subsequent csPCa after a negative biopsy in the current MRI-driven diagnostic pathway, such schemes should not be routinely used [480].

*5.7.3 **Seminal vesicle biopsy***

Indications for SV (staging) biopsies are poorly defined. At a PSA of > 15ng/mL, the odds of tumour involvement are 20–25% [481]. A SV staging biopsy is only useful if it has a decisive impact on treatment, such as ruling out radical tumour resection or for potential subsequent RT. Its added value compared with MRI is questionable.

*5.7.4 **Transition zone biopsy***

Transition zone sampling during baseline biopsies has a low detection rate and should be limited to MRI detected lesions or repeat template biopsies [482].

5.8 Diagnosis - Clinical Staging

*5.8.1 **T-staging***

The cT category listed in Table 4.1 relies only on DRE findings. Imaging parameters and biopsy results for local staging are, so far, not part of the T staging (within TNM) and the EAU risk category stratification [483].

5.8.1.a Ultrasound-based techniques and computed tomography

Transrectal US has limited accuracy for PCa local staging [484]. More advanced US-based techniques have not yet been tested in large-scale studies. In case of locally advanced cancers, abdominopelvic US or CT may show rectal or bladder invasion and dilatation of the upper collecting systems [484].

5.8.1.b Magnetic resonance imaging

T2-weighted imaging remains the most useful method for local staging on MRI. Pooled data from a meta-analysis showed a sensitivity and specificity of 0.57 (95% CI: 0.49–0.64) and 0.91 (95% CI: 0.88–0.93); 0.58 (95% CI: 0.47–0.68) and 0.96 (95% CI: 0.95–0.97); and 0.61 (95% CI: 0.54–0.67) and 0.88 (95% CI: 0.85–0.91), for EPE, SVI, and overall stage T3 assessment, respectively [485]. Similar results, with low sensitivity and good specificity have also been found in more recent large series [486-488].

Traditionally, EPE/SVI is assessed visually using qualitative signs (e.g. capsular disruption, visible tumour within periprostatic fat). Inter-reader agreement with such subjective reading is moderate, with kappa values ranging

from 0.41 to 0.68 [489]. The length of tumour capsule contact (LCC) is also a significant predictor of EPE. It has the advantage of being quantitative, although the ideal cut-off value remains debated [490, 491]. Several grading systems combining subjective qualitative signs and/or LCC into a score have shown good sensitivity (0.64-0.82) and specificity (0.64-0.93) for EPE, with substantial inter-reader agreement (κ = 0.56-0.74). None of these scores has shown definitive superiority over the others [492, 493].

Magnetic resonance imaging findings can improve the prediction of the pathological stage when combined with clinical and biopsy data. As a result, several groups developed multivariate risk calculators for predicting EPE/SVI or positive surgical margins [494]. These tools are particularly helpful when MRI does not show EPE/SVI due to its low sensitivity in the presence of microscopic EPE in patients with other aggressive disease features. In external validation cohorts, these risk calculators showed significantly better discrimination than nomograms without MRI-based features [495, 496].

Simple MRI features such as the tumour PI-RADS score, diameter or ADC value, or ECE/SVI features are strong predictors of BCR, alone or in combination with clinical data [497]. In 552 men treated by RP at seven different Dutch centres, MRI showed significantly higher sensitivity (51% vs. 12%; $p < 0.001$), and lower specificity (82% vs. 97%; $p < 0.001$) than DRE for non-organ-confined disease. All risk groups redefined using MRI findings rather than DRE findings showed better BCR-free survival due to improved discrimination and the Will Rogers phenomenon [498]. In one study of 604 patients who underwent RP at a single centre, the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) model obtained similar results in predicting BCR after RP when the pathological EPE or SVI data were replaced by MRI-based EPE or SVI assessment. Additionally, among the patients with pathological T3 disease, RFS was better for those without T3 disease on MRI than for those with T3 disease [487].

Given its low sensitivity for focal (microscopic) EPE, MRI is not recommended for local staging in low-risk patients. However, MRI can still be useful for treatment planning.

*5.8.2 **N staging***

5.8.2.a Computed tomography and MRI

Abdominal CT and T1-T2-weighted MRI indirectly assess nodal invasion by using LN diameter and morphology. However, the size of nonmetastatic LNs varies widely and may overlap the size of LN metastases. Usually, LNs with a short axis > 8mm in the pelvis and > 10mm outside the pelvis are considered malignant. Decreasing these thresholds improves sensitivity but decreases specificity. As a result, the ideal size threshold remains unclear [499, 500]. Computed tomography and MRI sensitivity is less than 40% [501]. Detection of microscopic LN invasion by CT is < 1% in patients with ISUP grade group < 4 cancer, PSA < 20ng/mL or localised disease [499, 502].

5.8.2.b Risk calculators incorporating MRI findings and clinical data

Computed tomography and MRI lack sensitivity for direct detection of positive LNs. Different risk calculators and nomograms which combine clinical data, systematic and/or MRI-targeted biopsy results and, for some of them, MRI findings have been developed and externally validated to estimate the risk of patients harbouring positive LNs [503-507]. The use of these models requires the adoption of arbitrary cut-offs, which reflect a balance between the risk of missing positive nodes and the additional operative time and potential complications of PLND. The application of commonly proposed thresholds is associated with limited specificity, leading to a considerable proportion of patients undergoing potentially unnecessary PLND, particularly in settings with low prevalence of LNI.

5.8.2.c Prostate-specific membrane antigen-based PET/CT

PSMA is an attractive target because of its specificity for prostate tissue, even if the expression in other non-prostatic malignancies or benign conditions may cause incidental false-positive findings [508, 509].

A multicentre prospective phase III imaging trial investigating men with intermediate- and high-risk PCa who underwent RP and PLND showed a sensitivity and specificity of ^{68}Ga-PSMA-11 PET of 0.40 (95% CI: 0.34-0.46), and 0.95 (95% CI: 0.92-0.97), respectively [510]. This is in line with previous results from prospective, multicentre studies addressing the accuracy of ^{68}Ga-PSMA and ^{18}F-DCFPyL PET/CT for LN staging in patients with newly diagnosed PCa [511-513]. Prostate-specific antigen may be a predictor of a positive PSMA PET/CT. In the primary staging cohort from a meta-analysis; however, no robust estimates of positivity were found [514].

A comparison between PSMA PET/CT and MRI was performed in a SR and meta-analysis including 13 studies (n = 1,597) [515]. ^{68}Ga-PSMA was found to have a higher sensitivity and a comparable specificity for staging preoperative LN metastases in intermediate- and high-risk PCa [516].

PSMA PET/CT has a good sensitivity and specificity for LN involvement, possibly impacting clinical decision-making. In an SR and meta-analysis including 37 studies, a subgroup analysis was performed in patients undergoing PSMA PET/CT for primary staging. On a per-patient-based analysis, the sensitivity and specificity of ^{68}Ga-PSMA PET were 77% and 97%, respectively, after eLND at the time of RP. On a per-lesion based analysis, sensitivity and specificity were 75% and 99%, respectively [514].

In summary, PSMA PET/CT is more sensitive in N staging as compared to MRI or abdominal contrast-enhanced CT. However, small LN metastases, under the spatial resolution of PET, may still be missed.

5.8.2.d Risk calculators incorporating MRI and PSMA findings

An international, multicentre study incorporated PSMA PET into existing nomograms to predict pelvic LN metastatic disease in PCa patients. Performance of three nomograms was assessed in 757 patients undergoing RARP and ePLND. The addition of PSMA PET to the nomograms substantially improved the discriminative ability of the models, yielding cross-validated AUCs of 0.76 (95% CI: 0.70–0.82), 0.77 (95% CI: 0.72–0.83) and 0.82 (95% CI: 0.76–0.87), respectively [517]. The same group developed a nomogram incorporating staging MRI and PSMA PET findings to predict LN metastases in a contemporary cohort of 700 patients from the Netherlands, who underwent RP and ePLND. The nomogram was then tested in 305 patients who underwent RP and ePLND at two centres in Australia. On this external cohort, the nomogram performed significantly better than the Briganti 2017 and the MSKCC nomograms. Its performance was similar to that of the Briganti 2019 nomogram [518]. However, given the excellent specificity of PSMA PET, it remains unclear whether a nomogram is required in patients with PSMA PET-positive lesions.

New models have been developed and externally validated in patients with negative PSMA PET, with the aim of identifying those at risk of harbouring micrometastatic disease undetectable by this modality due to its spatial resolution (≈5 mm) [507, 519].

5.8.2.e Surgical techniques

5.8.2.e.1 Pelvic lymph node dissection

Extended PLND 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, and the nodes medial and lateral to the internal iliac artery. Metastatic LN deposits, usually small volume, missed by modern imaging can be detected with ePLND [510]. Extended PLND is able to obtain higher LN yield and LN positivity compared to limited PLND [520]. As such, ePLND is a staging procedure that provides accurate information to guide management and prognostication [521].

There has been significant interest in whether this would also improve clinical outcomes. However, a meta-analysis demonstrated that performing PLND during RP failed to improve oncological outcomes, including survival [522]. Moreover, two RCTs show no benefit of ePLND versus limited PLND in terms of freedom from biochemical recurrence [523, 524]. After additional follow-up, a secondary report from the largest RCT did demonstrate a lower rate of distant metastasis, even though the median number of lymph nodes removed was similar in the two arms (12 vs. 14) and the proportions of patients with an involved lymph node were also comparable (11% vs. 13%) between the arms [523]. In addition, these updated results confirmed the lack of effect of ePLND on the development of biochemical recurrence or local pelvic nodal recurrence.

Furthermore, drivers of oncological differences were largely in the pN1 group, where a rapid event rate was observed, where PSMA PET is most likely to detect metastases either preoperatively or postoperatively if associated with a persistent PSA [525].

5.8.2.e.2 Complications of extended pelvic lymph node dissection

Extended PLND increases morbidity in the treatment of PCa [521]. In a SR and meta-analysis of postoperative complications after RP, 31.5% of reported complications were due to lymphocele, with 10% requiring surgical/percutaneous drainage [526]. Contemporary ePLND-related RCTs indicate ongoing variation in symptomatic lymphocele rates (0.9% - 9.7%) [527, 528], with a large RCT of peritoneal flap after ePLND reporting an 8% rate of lymphocele requiring drainage [529]. The extent of PLND also increases the risk of lymphocele formation (RR: 1.77, 95% CI: 1.45-2.16, $p < 0.0001$) [526]. When performed in the same patient but randomised to ePLND or limited PLND on each side, side-specific ePLND complications (compared to limited PLND) were 8.1% versus 2.4% ($p = 0.08$) [530]. Thromboembolic events are also more common with a meta-analysis suggesting that PLND increases the risk of thromboembolic disease by a factor of 2.8 in comparison to no PLND [531]. Lastly, an SR and meta-analysis, among all complications (14.1% overall), those “likely” to be related to PLND included DVT (2.8%), PE (2.1%), pelvic haematoma (2.6%) and lymphoedema (1.5%) [526].

Data on patient reported outcomes following ePLND are lacking. Available data suggests that these harms impact QoL, with the LAPPRO trial reporting significantly higher rates of lymphoedema following PLND versus no PLND (4.5% vs. 1.4%, RR: 2.7 95% CI: 1.2-6.3 p = 0.014), numerically worse in the ePLND group versus limited PLND (6.8% vs. 2.1%, RR: 3.4 95% CI: 0.6-19.0 p = 0.16), which translated to a worse overall QoL (adjusted for incontinence and erectile dysfunction) as reported by patients at three months (10.7% moderate/much bother, RR: 1.5 95% CI: 1.2-2.0 p < 0.001) and clinicians at 12 months (worse QoL 13.5%, RR: 5.7 95% CI: 1.9-16.4 p = 0.002) but not at 24 months (worse QoL 5.7%, RR: 0.8 95% CI: 0.1-6.1 p = 0.83) [532]. Lymphoedema is also more likely after ePLND followed by postoperative pelvic RT, than either treatment in isolation [533].

Despite some staging advantages, it is difficult to define which patients may benefit from ePLND owing to the lack of proof of an oncological benefit, with a significant risk of morbidity. The incorporation of PSMA PET/CT into clinical practice reduces the gap between imaging and pathological staging to fundamentally alter the risk/benefit ratio. Novel nomograms that incorporate imaging (MRI, PSMA PET/CT) can be used, particularly with a negative PSMA PET/CT but high risk of metastasis. It is unclear whether ePLND first with a subsequent adjuvant/salvage approach, or no ePLND with PSA- or imaging-guided postoperative treatment is superior in terms of oncological outcomes. Before offering ePLND, clinicians should discuss the uncertainties regarding the benefits and possible advantage of detecting low-volume nodal disease via ePLND and how this may impact postoperative management against the risks and harms associated with ePLND.

5.8.2.e.3 Strategies to reduce complications of extended pelvic lymph node dissection

Lymphocele complications might be reduced by incorporation of a peritoneal interposition flap, with a SR of RCTs reporting reduced symptomatic lymphocele (OR: 0.46, 95% CI: 0.23–0.93), overall lymphocele (OR: 0.51, 95% CI: 0.38–0.68) and Clavien-Dindo ≥ 3 complications (OR: 0.41, 95% CI: 0.22–0.85) without major function impairment [471]. The PELYCAN trial (n = 551) supported the benefits of bilateral peritoneal interposition flaps compared to no flap in reducing symptomatic lymphocele (3.7% vs. 9.1%, p = 0.005) and asymptomatic lymphocele (10.3% vs. 27.2%, p < 0.001) without compromise in postoperative complications at the expense of longer operating time (11 minutes, p < 0.001) [472]. However, a large trial of 1,080 patients reported no difference in symptomatic (requiring intervention; 7.2% vs 8.8%, p = 0.4) and radiological (29.5% vs 34.5%, p = 0.4) lymphocele rates when a peritoneal flap was used compared to none, nor any differences in complications or functional outcomes [529].

5.8.2.e.4 Lymph-node-positive patients during radical prostatectomy

Although no RCTs are available, data from prospective cohort studies comparing survival of pN+ patients (as defined following pathological examination after RP) support that RP may have a survival benefit over abandonment of RP in node-positive cases [534]. Consequently, there is no role for performing frozen section of suspicious LNs.

5.8.2.e.5 Sentinel node biopsy analysis

The rationale for a sentinel node biopsy (SNB) is based on the concept that a sentinel node is the first to be involved by migrating tumour cells. Therefore, if this node is negative, an ePLND can be avoided [535]. Intraprostatic injections of indocyanine green (ICG) have been used to visualise prostate-related LNs for SNB. A randomised comparison found more cancer-containing LNs in men who underwent a PLND guided by ICG but no difference in BCR at 22.9-month follow-up [536]. An SR of 21 studies showed a sensitivity of 95.2% and NPV of 98.0% for SNB in detecting men with metastases at ePLND [537]. An SR and meta-analysis of 13 studies reported high per-patient sensitivity (0.87) and NPV (0.95) rates, but at a “per node” level the sensitivity (0.53) dropped but NPV (0.96) and detection rate (0.92) was maintained [538]. However, this review was hampered by widespread heterogeneity of both definitions and how SNB is performed. This prompted the development of an expert consensus report to guide further research [535]. A randomised trial reported on ICG-only PLND (ICG-stained lymph nodes only, following preoperative injection of ICG into bilateral transition zones) compared to ePLND in 108 patients undergoing RP following staging with conventional imaging [539]. Operative time, lymph node counts (median 24 vs. 7) and postoperative lymphoedema (RR: 4.75, p < 0.05) were higher in the ePLND group but pN1 (ePLND 22% vs. ICG-PLND 28%, p = 0.7) and 24-month BCR-free survival (ePLND 83% vs. ICG-PLND 75%, p = 0.58) rates were similar between the groups.

The prospective SENTINELLE study investigated the diagnostic accuracy of sentinel lymph node biopsy-guided lymph node dissection (following intraprostatic injection of [99m]Tc-nanocolloid) compared to extended pelvic LN dissection in patients with intermediate- or high-risk prostate cancer. Sensitivity, specificity, NPV and positive predictive value of the SNB method in detecting patients with at least one LN metastasis were 95.4% (95% CI: 75.1-99.7), 100% (95% CI: 96.6-100), 99.2% (95% CI: 95.5-99.9) and 100% (95% CI: 80.7-100), respectively [545].

An emerging alternative to sentinel node removal following intraprostatic injections is PSMA-guided lymph node dissection following intravenous radioisotope injection and intraoperative radio guidance or optical guidance [540]. Initial studies report high specificity approaching 100%, although limited sensitivity and associated poor negative predictive value restrict the functional value at this point.

*5.8.3 **M staging***

5.8.3.a Bone scan

99mTc-bone scan is a highly sensitive conventional imaging technique, evaluating the distribution of active bone formation in the skeleton related to malignant and benign disease. A meta-analysis showed combined sensitivity and specificity of 79% (95% CI: 73–83%) and 82% (95% CI: 78–85%) at patient level [541]. Bone scan diagnostic yield is significantly influenced by the PSA level, the clinical stage and the tumour ISUP grade group [499, 542]. A retrospective study investigated the association between age, PSA and GS in 703 newly diagnosed PCa patients who were referred for bone scintigraphy. The incidence of bone metastases increased substantially with rising PSA and upgrading GS [543]. In two studies, a dominant Gleason pattern of four was found to be a significant predictor of positive bone scan [544, 545]. Bone scanning should be performed in symptomatic patients, independent of PSA level, ISUP GG or clinical stage [499]. Nevertheless, bone scintigraphy reveals low specificity (64.5%) and positive predictive value (55.4%), with a relatively low interobserver agreement [546]. Additional single-photon emission computed tomography (SPECT) using ^{99m}Tc-diphosphonates may overcome these limitations, by improved discrimination of benign and equivocal findings. In a multicentre phase III trial in patients with high-risk prostate or breast cancer, SPECT exhibited a sensitivity, specificity, and PPV of 63.3%, 87.5% and 78.4%, respectively [547].

5.8.3.b Fluoride PET/CT and MRI

^{18}F-sodium fluoride (^{18}F-NaF) PET or PET/CT, similarly to bone scintigraphy, only assesses the presence of bone metastases. The tracer was reported to have similar specificity and superior sensitivity to bone scintigraphy for detecting bone metastases in patients with newly diagnosed high-risk PCa [548, 549]. Interobserver agreement for the detection of bone metastases was excellent, demonstrating that ^{18}F-NaF PET/CT is a robust tool for the detection of osteoblastic lesions in patients with PCa [550].

Diffusion-weighted whole-body and axial skeleton MRI are more sensitive than bone scintigraphy and targeted conventional radiography in detecting bone metastases in high-risk PCa. Whole-body MRI can also detect visceral and nodal metastases, having been shown to be more sensitive and specific than combined bone scintigraphy, targeted radiography and abdominopelvic CT [551].

5.8.3.c PSMA PET/CT

A SR including 12 studies (n = 322) reported high variation in ^{68}Ga-PSMA PET/CT sensitivity for initial staging (range 33–99%; median sensitivity on per-lesion analysis 33–92%, and on per-patient analysis 66–91%), with good specificity (per-lesion 82–100%, and per-patient 67–99%), with most studies demonstrating increased detection rates with respect to conventional imaging modalities (bone scan and CT) [552].

In a prospective multicentre study in patients with high-risk PCa before curative surgery or RT (ProPSMA), 302 patients were randomly assigned to conventional imaging or ^{68}Ga-PSMA-11 PET/CT [553]. The primary outcome focused on the accuracy of first-line imaging for the identification of pelvic LN or distant metastases. Accuracy of ^{68}Ga-PSMA PET/CT was 27% (95% CI: 23–31) higher than that of CT and bone scintigraphy (92% [95% CI: 88–95] vs. 65% [95% CI: 60–69]; p < 0.0001). Conventional imaging had a lower sensitivity (38% [95% CI: 24–52] vs. 85% [95% CI: 74–96]) and specificity (91% [95% CI: 85–97] vs. 98% [95% CI: 95–100]) than PSMA PET/CT. Furthermore, ^{68}Ga-PSMA PET/CT scan prompted management change more frequently as compared to conventional imaging (41 [28%] men [95% CI: 21–36] vs. 23 [15%] men [95% CI: 10–22], p = 0.08), with less equivocal findings (7% [95% CI: 4–13] vs. 23% [95% CI: 17–31]) and lower radiation exposure (8.4 mSv vs. 19.2 mSv; p < 0.001) [553].The comparison of whole-body MRI and PSMA PET/CT in detecting bone metastases has led to inconclusive opposite results in two small cohorts [516, 554].

The added prognostic value of presurgical PSMA-PET for BCR-Free Survival (FS), compared with the presurgical Cancer of the Prostate Risk Assessment (CAPRA) and postsurgical CAPRA-Surgery (CAPRA-S) scores, in patients with intermediate- to high-risk PCa treated with RP and PLND has been investigated [555]. During a 32-month (interquartile range 23.3–42.9) follow-up, 91/240 (38%) BCR events were observed. The addition of PSMA-PET N1/M1 status to the presurgical CAPRA score improved the risk assessment for BCR significantly in comparison with the presurgical CAPRA score alone (C-statistic 0.70 [0.64–0.75] vs 0.63 [0.57–0.69]; p < 0.001).

5.8.4 *Summary of evidence and practical considerations on initial N/M staging*

The field of non-invasive N- and M-staging of PCa patients is evolving very rapidly. Evidence shows that PSMA PET/CT and whole-body MRI provide a more sensitive detection of LN and bone metastases than the classical work-up with bone scan and abdominopelvic CT. Initial results of a follow-up study of the surgical cohort in the multicentre prospective phase III imaging trial demonstrate that presurgical PSMA-PET is a strong prognostic biomarker, improving BCR-FS risk assessment [555]. However, the ideal management of patients diagnosed as metastatic by these more sensitive tests is yet unknown [556].

5.8.5 *Recommendations for staging of prostate cancer*

Recommendations	Strength rating
Any risk group staging	
Use prebiopsy magnetic resonance imaging (MRI) for local staging information.	Weak
Low-risk and favourable intermediate-risk localised disease	
Do not use additional imaging for staging purposes.	Strong
Unfavourable intermediate-risk disease	
Perform prostate-specific antigen positron emission tomography/computed tomography (PSMA PET/CT), if available, to increase accuracy, or at least cross-sectional abdominopelvic imaging and a bone scan.	Weak
High-risk localised disease/locally advanced disease	
Perform metastatic screening using PSMA PET/CT, if available, or at least cross-sectional abdominopelvic imaging and a bone-scan.	Strong

6. TREATMENT

This chapter reviews the available treatment modalities, followed by individual sections addressing treatment for the various disease stages.

6.1 Estimating life expectancy and health status

6.1.1 *Introduction*

Evaluation of life expectancy and health status is important in clinical decision-making for early detection, diagnosis and treatment of PCa. Prostate cancer is common in older men (median age 68 years) and diagnoses in men > 65 years will result in a continued increase in annual diagnosis in Europe and the USA associated with an aging population [557, 558].

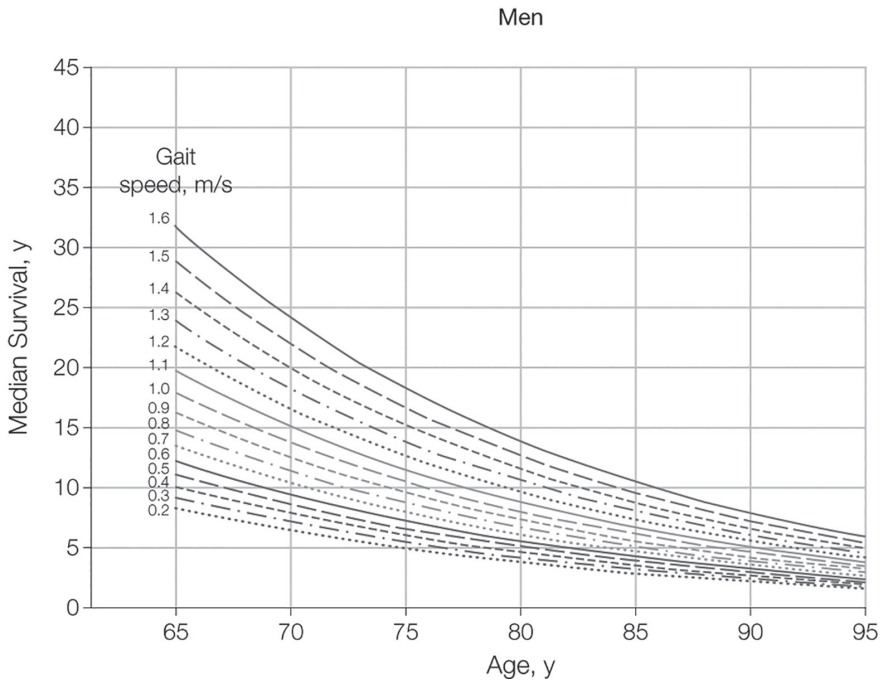
Active treatment mostly benefits patients with intermediate- or high-risk PCa and longest expected survival. In localised disease, over ten years' life expectancy is considered mandatory for any benefit from local treatment, and an improvement in CSS may take longer to become apparent. Older age and worse baseline health status have been associated with a smaller benefit in PCSM and life expectancy of surgery versus AS [559]. Although in an RCT the benefit of surgery with respect to death from PCa was largest in men < 65 years of age (RR: 0.45), RP was associated with a reduced risk of metastases and use of androgen deprivation therapy (ADT) also among older men (RR: 0.68 and 0.60, respectively) [560]. External beam RT shows similar cancer control regardless of age, assuming a dose of > 72Gy when using intensity-modulated or image-guided RT [561].

Older men have a higher incidence of PCa and may be undertreated despite the high overall mortality rates [562, 563]. Of all PCa-related deaths, 71% occur in men aged > 75 years [564], probably due to the higher incidence of advanced disease and death from PCa despite higher death rates from competing causes [565-567]. In the United States, only 41% of patients aged > 75 years with intermediate- and high-risk disease received curative treatment compared to 88% aged 65–74 [568].

6.1.2 *Life expectancy*

Life expectancy tables for European men are available online: https://ec.europa.eu/eurostat/. Survival may be variable, therefore estimates of survival must be individualised. Gait speed is a good single predictive method of life expectancy (from a standing start, at usual pace, generally over six meters). For men at age 75, ten-year survival ranged from 19% < 0.4 m/s to 87%, for ≥ 1.4 m/s [569].

Figure 6.1: Predicted median life expectancy by age and gait speed for males* [569]



**From Studenski S. et al. JAMA 2011 305(1)50, figure reproduced with permission of the publisher.*

6.1.3 Health status screening

Heterogeneity in performance increases with advancing age, therefore, it is important to use measures other than age or performance status (PS) alone when considering treatment options. The International SIOG PCa Working Group recommends that treatment for adults over 70 years of age should be based on a systematic evaluation of health status using the Geriatric 8 (G8) screening tool (Table 6.1.1) [159]. This tool helps to discriminate between those who are fit and those with frailty - a syndrome of reduced ability to respond to stressors. Patients with frailty have a higher risk of mortality and negative side effects of cancer treatment [570]. Healthy patients with a G8 score > 14 or vulnerable patients with reversible impairment after resolution of their geriatric problems should receive the same treatment as younger patients. Frail patients with irreversible impairment should receive adapted treatment. Patients who are too ill should receive only palliative treatment (see Figure 5.3) [159]. Patients with a G8 score ≤ 14 should undergo a comprehensive geriatric assessment (CGA), because this score is associated with three-year mortality. A CGA is a multi-domain assessment that includes comorbidity, nutritional status, cognitive and physical function and social supports to determine if impairments are reversible [571]. An SR of the effect of geriatric evaluation for older cancer patients showed improved treatment tolerance and completion [572].

The Clinical Frailty Scale (CFS) is another screening tool for frailty (see Figure 5.4) [573]. Although not frequently used in the cancer setting, the CFS is considered a common language for expressing degree of frailty. The scale runs from one to nine, with higher scores indicating increasing frailty. Patients with a higher CFS score have a higher 30-day mortality after surgery and are less likely to be discharged home [574].

It is important to use a validated tool to identify frailty, such as the G8 or CFS, as clinical judgement has been shown to be poorly predictive of frailty in older patients with cancer [575].

6.1.3.a Co-morbidity

Co-morbidity is a major predictor of non-cancer-specific death in localised PCa treated with RP and is more important than age [576, 577]. Ten years after watchful waiting for PCa, most men with a high co-morbidity score had died from competing causes, irrespective of age or tumour aggressiveness [576]. Measures for co-morbidity include: Cumulative Illness Score Rating-Geriatrics (CISR-G) [578, 579] (Table 6.1.2) and Charlson Co-morbidity Index (CCI) [580].

6.1.3.b Nutritional status

Malnutrition can be estimated from body weight during the previous three months (good nutritional status < 5% weight loss; risk of malnutrition: 5–10% weight loss; severe malnutrition: > 10% weight loss) [581].

6.1.3.c Cognitive function

Cognitive impairment can be screened for using the mini-COG (https://mini-cog.com/), which consists of three-word recall and a clock-drawing test and can be completed within five minutes. A score of ≤ 3/5 indicates the need to refer the patient for full cognitive assessment. Patients with any form of cognitive impairment (e.g. Alzheimer's or vascular dementia) may need a capacity assessment of their ability to make an informed decision, which is an increasingly important factor in health status assessment [582-584]. Cognitive impairment also predicts risk of delirium, which is important for patients undergoing surgery [585].

6.1.3.d Physical function

Measures for overall physical functioning include: Karnofsky score and ECOG scores [586]. Measures for dependence in daily activities include Activities of Daily Living (ADL; basic activities) and Instrumental Activities of Daily Living (IADL; activities requiring higher cognition and judgement) [587-589].

6.1.3.e Shared decision-making

The patient's own values and preferences should be considered as well as the above factors. A shared decision-making process also involves anticipated changes to QoL, functional ability and a patient's hopes, worries and expectations about the future [590]. Particularly in older and frail patients, these aspects should be given equal importance to disease characteristics during the decision-making process [591]. Older patients may also wish to involve family members, and this is particularly important where cognitive impairment exists.

6.1.4 Conclusion

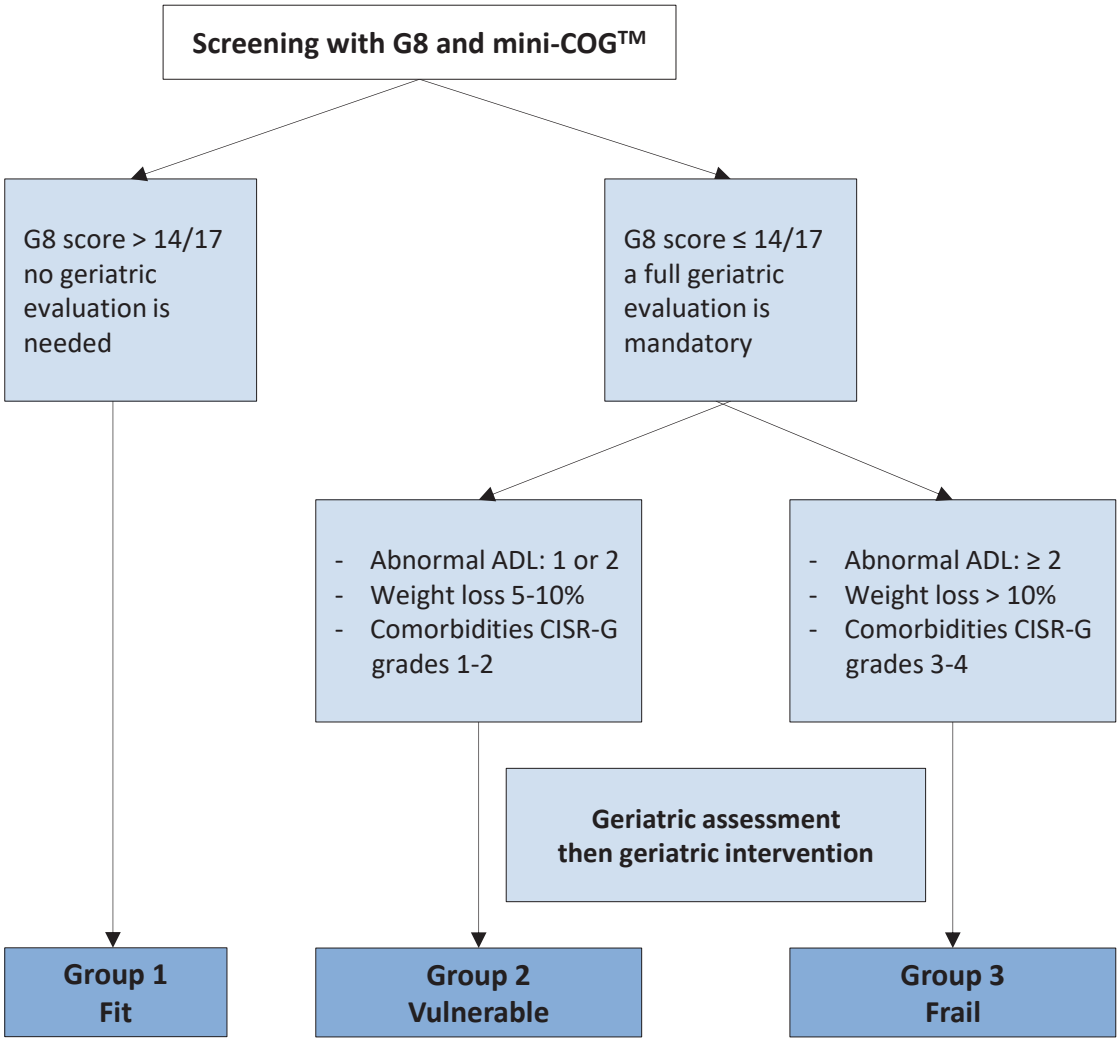
Individual life expectancy, health status, frailty and co-morbidity, not age alone, should be central in clinical decisions on screening, diagnostics, and treatment for PCa. A life expectancy of ten years is most commonly used as a threshold for benefit of local treatment. Older men may be undertreated. Patients aged 70 years or older who have frailty should receive a comprehensive geriatric assessment. Resolution of impairments in vulnerable men allows a similar urological approach as in fit patients.

Table 6.1.1: G8 screening tool (adapted from [592])

	Items	Possible responses (score)
A	Has food intake declined over the past three months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 = severe decrease in food intake
		1 = moderate decrease in food intake
		2 = no decrease in food intake
B	Weight loss during the last three months?	0 = weight loss > 3 kg
		1 = does not know
		2 = weight loss between 1 and 3 kg
		3 = no weight loss
C	Mobility?	0 = bed- or chair-bound
		1 = able to get out of bed/chair but does not go out
		2 = goes out
D	Neuropsychological problems?	0 = severe dementia or depression
		1 = mild dementia
		2 = no psychological problems
E	BMI? (weight in kg)/(height in m)	0 = BMI < 19
		1 = BMI 19 to < 21
		2 = BMI 21 to < 23
		3 = BMI ≥ 23
F	Takes more than three prescription drugs per day?	0 = yes
		1 = no

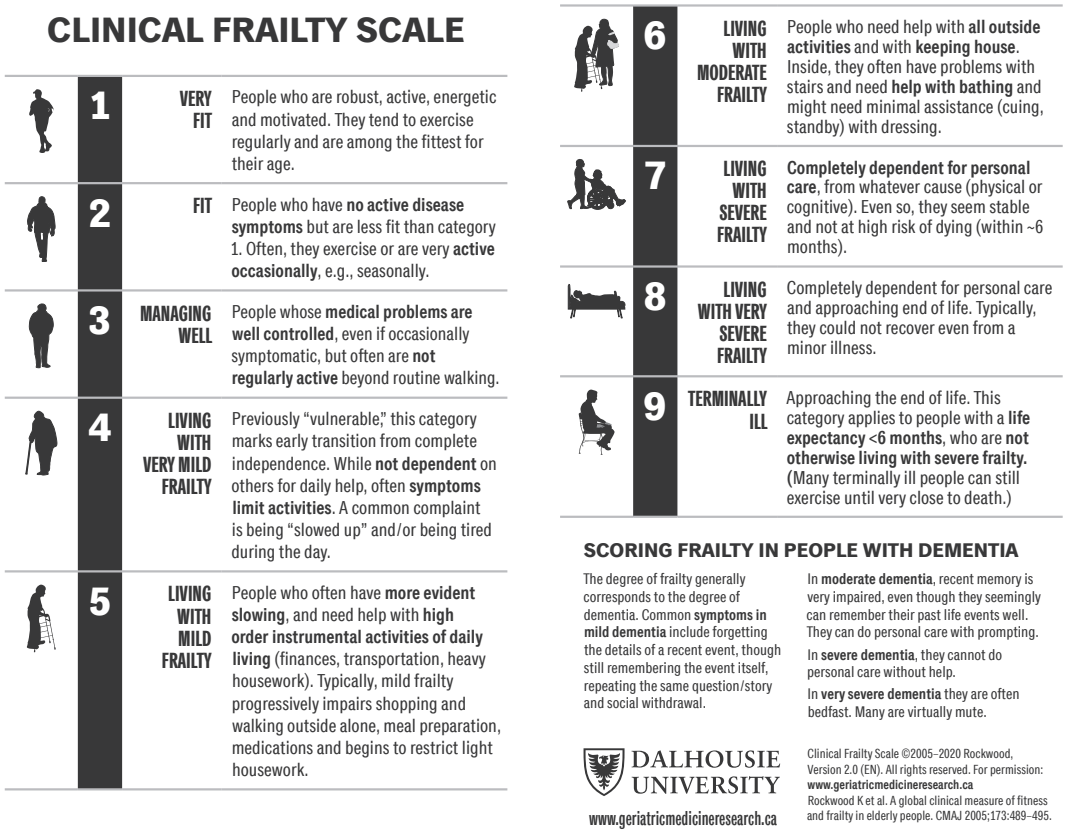
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = not as good
		0.5 = does not know
		1.0 = as good
		2.0 = better
H	Age	0 = ≥ 85
		1 = 80-85
		2 = < 80
	Total score	**0-17**

Figure 6.2: Decision tree for health status screening (men > 70 years)* [159]



ADLs = activities of daily living; CGA = comprehensive geriatric assessment; CIRS-G = Cumulative Illness Rating Score - Geriatrics; Mini-COG™ = Mini-COG™ cognitive test.
** For Mini-COG™, a cut-off point of ≤ 3/5 indicates a need to refer the patient for full evaluation of potential dementia. From Boyle H.J., et al. Eur J Cancer 2019:116; 116 [159], reproduced with permission of Elsevier.*

Figure 6.3: The Clinical Frailty Scale version 2.0 [573]*



**Permission to reproduce the CFS was granted by the copyright holder.*

Table 6.1.2: Cumulative Illness Score Rating-Geriatrics (CISR-G)

1	Cardiac (heart only)
2	Hypertension (rating is based on severity; affected systems are rated separately)
3	Vascular (blood, blood vessels and cells, marrow, spleen, lymphatics)
4	Respiratory (lungs, bronchi, trachea below the larynx)
5	ENT (eye, ear, nose, throat, larynx)
6	Upper GI (oesophagus, stomach, duodenum. Biliar and pancreatic trees; do not include diabetes)
7	Lower GI (intestines, hernias)
8	Hepatic (liver only)
9	Renal (kidneys only)
10	Other GU (ureters, bladder, urethra, prostate, genitals)
11	Musculoskeletal-Integumentary (muscles, bone, skin)
12	Neurological (brain, spinal cord, nerves; do not include dementia)
13	Endocrine-Metabolic (includes diabetes, diffuse infections, infections, toxicity)
14	Psychiatric/Behavioural (includes dementia, depression, anxiety, agitation, psychosis)
	All body systems are scores on a 0 - 4 scale. 0: No problem affecting that system. 1: Current mild problem or past significant problem. 2: Moderate disability or morbidity and/or requires first line therapy. 3: Severe problem and/or constant and significant disability and/or hard to control chronic problems. 4: Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.
Total score 0-56	

6.1.5 Recommendations for evaluating health status and life expectancy

Recommendations	Strength rating
Use individual life expectancy, health status and comorbidity in PCa management.	Strong
Use the Geriatric 8 (G8), mini-COG and Clinical Frailty Scale tools for health status screening.	Strong
Perform a full specialist geriatric evaluation in patients with a G8 score ≤ 14.	Strong
Consider standard treatment in vulnerable patients with reversible impairments (after resolution of geriatric problems), similar to fit patients if life expectancy is > 10 years.	Weak
Offer adapted treatment or watchful waiting to patients with irreversible impairment.	Weak
Offer palliative symptom-directed therapy alone to frail patients.	Strong

6.2 Treatment modalities

6.2.1 Expectant management strategies

Two different strategies of expectant management are available watchful waiting (WW) and active surveillance (AS). The differences between WW and AS are presented in Table 6.2.1.

In patients with asymptomatic PCa in which curative therapy is not indicated due to a limited life expectancy based upon co-morbidities or age (<10 years) PCa may be managed conservatively and the patient followed until local or metastatic symptomatic progression occurs or is thought to be imminent. This approach is referred to as watchful waiting (WW). When predicting life expectancy co-morbidity is as important as age as it greatly increases the risk of dying from non-PCa-related causes. In an analysis of 19,639 patients aged > 65 years who were not given curative treatment, most men with a CCI (Charlson Comorbidity Index) score ≥ 2 had died from competing causes at ten years follow-up regardless of their age at time of diagnosis [576]. Tumour grade had little impact on OS suggesting that patients could have been spared biopsy and diagnosis of PCa. The oncological advantages of active treatment are unlikely to be relevant to them. This strategy maintains quality of life by delaying the side effects of palliative androgen deprivation therapy (ADT).

In patients with low- to intermediate-risk PCa, the natural course is so favourable that even in men with a long life-expectancy, curative local therapy may be postponed, or avoided altogether, by using active surveillance. Death from other causes is significantly more likely. In the ProtecT trial (see section 6.2.1.a), prostate cancer-related death was 3% at 15 years compared to death from any cause in 21.7% of patients - numbers that have been further validated in two large population-based studies from Canada and Sweden [593-595]. This occurs because the prevalence of cancer cells in the prostate is so much higher than the risk of developing clinical disease or dying from PCa. With the previous introduction of PSA, and now MRI, increased early detection of these small tumours there is a distinct risk of overdiagnosis and subsequent overtreatment of low- to intermediate-risk disease (Section 3.1 Epidemiology) [7, 596, 597]. Data from studies conducted on patients who did not undergo local treatment with long-term outcomes (up to 25 years) are available. The prognosis of low grade PCa is extremely favourable. Several series have shown a consistent CSS rate of 82–87% at ten years [598, 599], and 80–95% for T1/T2 and ISUP GG ≤ 2 PCa [600]. In three studies with data beyond 15 years, the reported CSS rates were 80%, 79% and 58% [598, 599, 601]. Two studies reported 20-year CSS rates of 57% and 32% [598, 601]. The observed heterogeneity in outcomes is due to different inclusion criteria, with some older studies from the pre-PSA era showing worse outcomes [601].

When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year PCSM rates of 13.0% and 19.6%, respectively [602]. Cancer survival rates are even higher. Patients with well-, moderately and poorly differentiated tumours had 10-year CSS rates of 91%, 90% and 74%, respectively, correlating with data from a pooled analysis [600]. In addition, many patients classified as ISUP GG 1 would now be classified as ISUP GG 2–3 based on the 2005 Gleason classification, and accurate biopsy targeting following the introduction of pre-biopsy MRI suggesting that the above-mentioned results should be considered as minimal and current outcomes would be more favourable.

In screen-detected localised PCa, there is also a lead-time bias, resulting in a higher rate of early detected PCa, but also an even higher risk of detecting clinically insignificant PCa that never would have caused any symptoms [597]. Cancer-specific survival from untreated screen-detected PCa in patients with ISUP grade groups 1–2 is therefore likely to be even more favourable than for PCa detected of other reasons. Consequently, a high proportion of men with PSA-detected PCa are suitable for conservative management.

This highlights the importance of assessing co-morbidity even before considering a biopsy, but also before advising a patient with a PCa diagnosis on the optimal treatment for them. Estimation of competing benefits of active vs. conservative treatment and death from any cause at ten and fifteen years can be estimated using the PREDICT Prostate tool (https://prostate.predict.nhs.uk/), which is endorsed by the National Institute for Health and Care Excellence in the UK [603].

Table 6.2.1: Differences between active surveillance and watchful waiting [478]

	Active surveillance	Watchful waiting
Treatment intent	Curative	Palliative
Follow-up	Predefined schedule	Patient-specific
Assessment/markers* used	DRE, PSA, rebiopsy, imaging (MRI)	• None (wait for symptoms); or • Annual/biannual PSA (consider DRE if significant PSA-rise or imaging if metastases suspected)
Life expectancy	> 10 years	< 10 years
Aim	Minimise curative treatment-related toxicity without compromising survival, as the PCa is so indolent that it is unlikely to cause symptoms even with long life expectancy	Minimise palliative treatment-related (ADT) toxicity without compromising survival, PCa is unlikely to affect lifespan.
Eligible patients	Low-risk and selected intermediate-risk patients	Can apply to patients in all risk groups

ADT - androgen deprivation therapy; DRE = digital rectal examination; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.
**Molecular markers and/or PSMA-PET/CT (MRI) may be used.*

6.2.1.a Watchful waiting

Traditionally, WW has meant waiting for symptoms of PCa to develop without any specific follow-up schedule. However, for patients with locally advanced disease, a PSA doubling time (PSA-DT) < 12 months, and PSA-values over 30-50ng/mL early hormonal treatment might prolong survival in a clinically relevant time frame [604, 605]. A more active follow-up of men on WW could therefore be beneficial for the higher risk groups (often associated with a higher ISUP GG), so that progression of local tumour or metastases can be detected and hormonal therapy initiated before they present with significant symptoms. The WW strategy should therefore be individualized. Biannual PSA, or annual PSA after a period of stable disease, followed by DRE or bone scan if PSA rises significantly, could then be of value.

In a Swedish registry study of men with nonmetastatic PCa on WW, after five years, 66.2% of patients with low-risk and 36.1% with high-risk disease, and 25.5% and 10.4% after ten years, were still alive and not receiving ADT [606]. At ten years, 4.1% and 10.8% had transitioned to castration-resistant disease, respectively. Importantly, 92.3% of low-risk patients and 84.1% of high-risk patients died due to causes other than PCa after ten years [606].

Watchful waiting vs. radical prostatectomy

Two RCTs and one Cochrane review have been published comparing the outcomes of WW to radical prostatectomy (RP). The SPCG-4 study was a RCT from the pre-PSA era, randomising patients into either WW or RP in 695 men (24% with nonpalpable disease) [607]. The study found RP to provide superior CSS, OS and progression-free survival (PFS) compared to WW at a median follow-up of 23.6 years (range 3 weeks to 28 years). However, the benefit in favour of RP over WW was only apparent after ten years.

The PIVOT trial, an RCT conducted in the early PSA era, made a similar comparison between RP versus WW in 731 men (50% with nonpalpable, 42% low-risk disease), but in contrast to the SPCG-4, it found little to no benefit of RP (cumulative incidence of all-cause death, RP vs. observation: 68% vs. 73%; RR: 0.92, 95% CI: 0.84–1.01) within a median follow-up period of 18.6 years (interquartile range, 16.6 to 20 years) [608]. Exploratory subgroup analysis showed that the borderline benefit from RP was most marked for intermediate-risk disease (RR: 0.84, 95% CI: 0.73–0.98), but there was no benefit in patients with low- or high-risk disease. Overall, no adverse effects on health related QoL (HRQoL) and psychological well-being was apparent in the first five years [609].

However, one of the criticisms of the PIVOT trial is the relatively high overall mortality rate in the WW group compared with more contemporary series, suggesting a selection bias.

A Cochrane review performed a pooled analysis of RCTs comparing RP versus WW [610]. Three studies were included: the previously mentioned SPCG-4 [607] and PIVOT [608], and the Veteran's Administration Cooperative Urological Research Group (VACURG) study, which was conducted in the pre-PSA era [611]. The authors found that RP compared with WW reduced time to death by any cause (HR: 0.79, 95% CI: 0.70–0.90), time to death by PCa (HR: 0.57, 95% CI: 0.44–0.73), and time to metastatic progression (HR: 0.56, 95% CI: 0.46–0.70) at 29-years follow-up. However, RP was associated with higher rates of urinary incontinence (RR: 3.97, 95% CI: 2.34–6.74) and ED (RR: 2.67, 95% CI: 1.63–4.38).

ProtecT study

ProtecT, randomised 1,643 patients into one of three arms: active treatment with either RP or EBRT or active monitoring (AM) with outcomes reported at ten years and 15 years [593, 612]. ProtecT trial did not apply a formal AS strategy. Active monitoring (AM) was a significantly less stringent surveillance strategy, using PSA only, with relaxed criteria to define progression. No repeat biopsies were performed as in AS.

At enrolment, 66% of the patients had low-risk disease, with 90% having a PSA < 10ng/mL, 77% ISUP GG 1 (20% ISUP GG 2–3) and 76% had T1c disease. The remaining patients had mainly intermediate-risk disease (approximately 40%).

The key finding was that AM was as effective as active treatment at 15 years (CSS = 96.9% in the AM-group vs. 97.8% in the RP group and 97.1% in the EBRT-group, p = 0.53), but has an increased metastatic progression risk (9.4% vs. 4.7% and 5.0%, respectively), as well as clinical progression at 15 years (25.9% for AM vs. 10.7% for RP/RT). Death from any cause occurred in 21.7% of the cohort, with similar numbers across treatment groups. Metastases, although rare, were more frequent than seen with comparable AS protocols [613]. A comprehensive characterisation of the ProtecT study cohort was performed after ten years, stratifying patients at baseline according to risk of progression using clinical stage, grade at diagnosis and PSA level [614]. Additionally, detailed clinicopathological information on participants who received RP were analysed.

The fifteen-year paper reported updated contemporary risk stratification according to D'Amico (24.1% Intermediate risk, 9.6% high risk), CAPRA (26.4% Score 3-5, 2.5% Score 6-10) and Cambridge Prognostic Group (20.5% Group 2, 8.8% Groups 3-5). Among patients who underwent RP, 50.5% were ISUP GG ≥2, while 28.5% had an increase in pathological stage, and 32% had an increase in tumour grade. Additionally, 51% of patients who developed metastases displayed ISUP GG 1 and 47.6% were low CAPRA risk. Over time, 61.1% of patients in the AM group received radical treatment (from 54.8% at ten years). Based on the ten-year report, the authors aimed to identify prognostic markers. The results showed that the following were associated with increased risk of disease progression (p < 0.001 for each):

- treatment received;
- age (65–69 vs. 50–64 years);
- PSA;
- ISUP GG at diagnosis;
- cT stage;
- risk group;
- number of PCa-involved biopsy cores;
- maximum length of tumour (median 5.0 vs. 3.0mm);
- aggregate length of tumour (median 8.0 vs. 4.0mm);
- presence of perineural invasion.

However, these factors could not reliably predict progression in individuals. Notably, 53% (n = 105) of patients who progressed had biopsy ISUP GG 1 disease, although, conversely, none of the participants who received RP and subsequently progressed had pathological ISUP GG 1 tumours. This discrepancy in progression and metastases rate between the AM arm of the ProtecT study and comparable AS protocols can most likely be explained by differences in intensity of surveillance, inadequate sampling by PSA testing and 10-core TRUS-guided biopsies.

Nevertheless, the ProtecT study has reinforced the role of deferred active treatment (i.e., either AS or some form of initial AM) as a feasible alternative to active curative interventions in all patients with low-grade and low-stage disease, as well as for many patients with favourable intermediate risk disease. Beyond 15 years, no RCT data are available yet, although AS is likely to give greater reassurance - particularly in younger men - based on more

accurate risk stratification at recruitment and more stringent criteria regarding follow-up, imaging, repeat biopsy and reclassification. Individual life expectancy must continuously be evaluated before considering any active treatment in low-risk patients and in those with up to ten to 15 years' individual life expectancy [614].

6.2.1.b Active surveillance

Active surveillance (AS) aims to avoid over-treatment in men with PCa, whilst allowing identification and appropriate intervention for those who show reclassification during follow-up [615]. Patients remain under close surveillance through structured surveillance programmes with regular follow-up consisting of PSA testing, clinical examination, repeat prostate biopsies and an increasing role of imaging (usually MRI). Curative treatment is prompted by predefined thresholds indicative of development to potentially significant disease that is still curable while considering individual life expectancy.

No formal RCT is available comparing AS to curative treatment. Several cohorts have investigated AS in organ-confined disease, the findings of which were summarised in a SR [613, 616]. Long term oncological outcomes of patients on AS are very favourable, with ten-year CSS rates of 98.1-100% and OS rates of 81-100% [612, 617-622]. Although many men remain treatment-free during extended follow-up, more than one- third of patients are reclassified during follow-up, most of whom undergo curative treatment due to disease upgrading, upstaging, or increase in disease extent, or patient preference.

6.2.1.b.1 Active surveillance - inclusion criteria

Active surveillance inclusion criteria aim to select cases with a favourable natural course of disease, and in whom, in case of reclassification, the delay caused by the initial expectant management strategy does not lead to additional unfavourable outcomes. There is variation and heterogeneity between studies regarding exact patient selection, eligibility criteria, and follow-up policies (including frequency of clinical follow-up, use of PSA kinetics, PSA-density, frequency of standard repeat prostate biopsies, frequency and type of imaging such as MRI, and type of biopsy strategy (systematic, MRI- lesion targeted biopsies, combinations, or template biopsies). For men diagnosed with EAU risk group low-risk PCa who have an adequate life expectancy, AS is the first management option. In classic AS cohorts, additional selection criteria were incorporated such as PSA-density thresholds or biopsy core involvement parameters. With developments in the diagnostic algorithm regarding prostate biopsy indication and biopsy core strategy (i.e. use of pre-biopsy risk calculators, MRI, and targeted biopsies), the case-mix of patients considered for AS is changing, as well as the availability of parameters used for risk stratification and AS eligibility and follow-up.

Guidance regarding selection and follow-up criteria for AS is limited by the lack of data from prospective RCTs. As a consequence, the international collaborative DETECTIVE study involving healthcare practitioners and patients developed consensus statements for deferred treatment with curative intent for localised PCa, covering all domains of AS [623], as well as a formal SR on the various AS protocols [624].

The most frequently applied criteria include: ISUP GG 1 (on systematic biopsy), clinical stage cT1c or cT2a, PSA < 10ng/mL and PSA-D < 0.15ng/mL/cc [613, 617]. The latter threshold remains controversial [617, 618]. These criteria were supported by the DETECTIVE study consensus. MRI index lesion diameter may provide additional guidance, as thresholds of > 10mm and > 20mm have been used to predict BCR after RP, but are not yet used in AS criteria [619]. The Movember consensus group, consisting of 27 healthcare professional and 12 lived-experience participants from across the world, agreed that ISUP GG and MRI were the most important criteria for determining eligibility to AS [620].

A SR and meta-analysis found three clinicopathological variables that were significantly associated with reclassification: high PSA-D, > 2 positive cores (on systematic biopsies), and African-American descent [621]. A review of the risk of progression for African-American men on AS also indicated a potential increased risk of progression, but the association was not strong enough to discourage African-American men from undergoing AS, but thorough confirmatory testing is important [625]. Another review reported an association between family history and upgrading (adjusted disease progression HR 1.31, p<0.0001), although the certainty of evidence was low, and had no significant impact on adverse pathology at prostatectomy, indicating this factor alone is not a contraindication for AS [626].

In addition, a previous pathology consensus group suggested excluding men from AS when any of the following features were present: cribriform histology, predominant ductal carcinoma (including pure IDC), sarcomatoid carcinoma, small cell carcinoma, EPE or LVI in needle biopsy [627], or perineural invasion [628].

In men eligible for AS based upon systematic biopsy findings alone who did not have a prebiopsy MRI, a re-biopsy within six to twelve months (usually referred to as 'confirmatory biopsy') is mandatory to exclude sampling error.

6.2.1.b.2 Active surveillance – inclusion of intermediate risk disease

The outcomes of AS in intermediate-risk PCa have been analysed in three SRs and meta-analyses, summarising available data on its oncological outcomes and comparing patients with intermediate-risk PCa to patients with low-risk disease [629-631]. The definition of AS was not strictly defined in either of the reviews. Instead, the search strategies included 'active surveillance' as a search term, and no a priori study protocol was available. There was significant clinical heterogeneity in terms of inclusion criteria for intermediate-risk disease and use of MRI.

The results showed the proportion of patients who remained on AS was comparable between the low- and intermediate-risk groups after ten- and fifteen-years' follow-up. Metastases-free survival did not significantly differ after five years (OR: 0.55, 95% CI: 0.2–1.53) but was worse in the intermediate-risk group after ten years (OR: 0.46, 95% CI: 0.28–0.77 and RR: 5.79, 95% CI: 4.61-7.29, respectively) [631]. Cancer-specific survival was worse in the intermediate-risk group after ten years (OR: 0.47, 95% CI: 0.31–0.69) and fifteen years (OR: 0.34; 95% CI: 0.2–0.58; RR: 3.93, 95% CI: 2.93-5.27, RR: 0.92, 95% CI: 0.89-0.96, respectively), although this is most likely due to less favourable baseline characteristics and not due to the delay caused by the initial period of AS. Overall survival was not statistically significantly different at five years' follow-up (OR: 0.84, 95% CI: 0.45–1.57) but was significantly worse in the intermediate-risk group after ten years (OR: 0.43; 95% CI: 0.35–0.53, RR: 1.44, 95% CI: 1.11-1.86, RR: 0.87, 95% CI: 0.82-0.93, respectively). In a subgroup analysis of four studies comparing outcomes of patients with low- and intermediate-risk PCa of ISUP GG ≤ 2 (n = 1,900) no statistically significant difference could be found in terms of treatment free survival or risk of developing metastases (RR: 1.03, 95% CI: 0.62-1.71 and RR: 2.09, 95% CI: 0.75-5.82, respectively). It should be noted that many of the studies included patients with ISUP GG 3 disease. When these studies were excluded no difference in treatment free, CSS or OS was observed [630].

These reviews indicate that AS, in unselected intermediate-risk patients, implies a higher risk of progression over time. It remains unclear whether this difference only reflects the baseline difference in outcome, that can also be seen when comparing immediate treatment of low- and intermediate-risk PCa, or if the delay in treatment caused any worsening of the outcomes in the intermediate-risk group in any way. All three reviews conclude that AS could be offered to patients with intermediate-risk disease, but they should be informed of a higher risk of progression and whilst one of the reviews specifically suggest limiting the inclusion of intermediate-risk patients to those with low-volume ISUP GG 2 disease [629].

A Canadian consensus group proposes that low volume ISUP GG 2 (< 10% Gleason pattern 4 on systematic biopsies) may also be considered for AS. These recommendations have been endorsed by the ASCO [306] and the DETECTIVE study consensus [623] for those patients with a PSA < 10ng/mL and low core positivity. The DETECTIVE study concluded that men with favourable ISUP GG 2 PCa (PSA < 10ng/mL, low PSA density, clinical stage ≤ cT2a and a low number of positive systematic cores) should also be considered for deferred treatment [623]. In this setting, re-biopsy within six to twelve months to exclude sampling error is even more relevant than in low-risk disease [617, 632]. The DETECTIVE study-related qualitative SR aimed to determine appropriate criteria for inclusion of intermediate-risk disease into AS protocols [624]. Out of 371 AS protocols included in the review, more than 50% included patients with intermediate-risk disease on the basis of PSA up to 20ng/mL (25.3%), ISUP GG 2 or 3 (27.7%), clinical stage cT2b/c (41.6%) and/or direct use of D'Amico risk grouping of intermediate risk or above (51.1%). The DETECTIVE study reached consensus that patients with ISUP GG 3, or patients with intraductal or cribriform histology, should not be considered for AS. The presence of any grade 4 pattern is associated with a threefold increased risk of metastases compared to ISUP GG 1, while a PSA up to 20ng/mL might be an acceptable threshold [632-634], especially in the context of low PSA-D.

The indicator of the tumour volume may be either the number of positive cores and the length of cancer in each core based on systematic biopsies, or the volume of the dominant lesion seen on mpMRI [623]. If targeted biopsies based upon mpMRI images are performed, the number of positive cores of the targeted biopsies are not an indicator of the extent of disease or tumour volume when considering a patient for AS due to the altered biopsy protocol.

MRI-targeted biopsies have been associated with upgrading of tumours, but improved outcomes [113].

The large prospective PRIAS study on AS expanded inclusion criteria when MRI and targeted systematic biopsies are used at inclusion (https://www.prias-project.org/):

- cT ≤ 2
- ISUP: GG 1 or GG 2 without invasive cribriform growth and intraductal carcinoma
- PSA: ≤ 20ng/mL
- PSA density: < 0.25ng/mL/cc
- Number of positive cores:
  - For ISUP GG 1: No limit.
  - For ISUP GG 2 (without invasive cribriform growth and intraductal carcinoma): ≤ 50% systematic cores (where multiple positive cores from the same lesion on MRI count for one positive core).

During follow-up, upgrading is the only criterium for discontinuation, defined as ISUP GG ≥ 3 or ISUP GG ≥ 2 with cribriform growth or intraductal carcinoma, or ISUP GG ≥ 2 with > 50% positive cores.

A multidisciplinary consensus conference on germline testing has suggested a genetic implementation framework for the management of PCa [185]. Based on consensus, *BRCA2* gene testing was recommended for AS discussions and could be performed in men with a family history of prostate, breast or ovarian cancers. However, the nature of such discussions and how a positive result influences management were beyond the scope of the project. Currently, *BRCA2* mutation does not exclude a patient from AS if tumour factors are otherwise favourable. Moreover, if included in AS programmes, patients with a known *BRCA2* mutation should be cautiously monitored until such time that more robust data are available.

6.2.1.b.3 Tissue-based prognostic biomarker testing for selection for AS

Biomarkers, including Oncotype Dx®, Prolaris®, Decipher®, PORTOS and ProMark®, are promising. However, further data and comparisons with other parameters (including MRI) will be needed before such markers can be used in standard clinical practice [635].

6.2.1.b.4 Magnetic resonance imaging for selection for active surveillance

Two RCTs and an SR showed that adding MRI-targeted biopsy to systematic sampling at confirmatory biopsy increased the number of cancers labelled ISUP GG ≥ 2 and thus may aid patient selection for AS, although the impact of MRI and targeted biopsies with corresponding stage shift on long-term oncological outcomes of AS is lacking [135, 636-641]. Adding MRI-targeted biopsy to systematic sampling at confirmatory biopsy improved upgrade detection by increments of 0-7.9 per 100 men depending on the series [636]. In a meta-analysis of six studies, the rate of upgrading to ISUP GG ≥ 2 cancer increased from 20% (95% CI: 16–25%) to 27% (95% CI: 22–34%) when MRI-targeted biopsy was added to systematic biopsy [641]. The Active Surveillance MRI Study (ASIST) randomised men on AS scheduled for confirmatory biopsy to either 12-core systematic biopsy or to MRI with targeted biopsy (when indicated), combined with systematic biopsy (up to 12 cores in total). After two years of follow-up, the use of MRI before confirmatory biopsy resulted in fewer failures of surveillance (19% vs. 35%, p = 0.017) and in fewer patients progressing to ISUP GG ≥ 2 cancer (9.9% vs. 23%, p = 0.048) [639]. However, systematic biopsy retains its added value, which argues for a combined biopsy approach [636, 641]. The DETECTIVE study agreed that men eligible for AS after combined systematic and MRI-targeted biopsy do not require a confirmatory biopsy; a recommendation further supported by the results of the MRIAS trial [623, 642].

If the PCa diagnosis is made on MRI-targeted biopsy alone to lower the risk of over detection of insignificant (see Section 5.4.1, and 5.4.2), and the number of positive systematic cores used as an indication for tumour volume during AS is not available, MRI lesion diameter can be used as a surrogate, although specific definitions have not yet been tested in an AS setting (e.g. for ISUP GG 2 tumours no PIRADS 5 or < 20mm lesion size) [619]. Several studies indicate that PSMA-PET-CT or PSMA-PET-MRI may have additional value to the above-mentioned clinicopathological variables for risk stratification before AS [136, 643]. Thus far, however, the studies are too small, the follow-up too short and association with long-term oncological outcomes is lacking to draw any hard conclusions and for this modality to be recommended outside of clinical trials.

6.2.1.b.5 Active surveillance follow-up

Based on the DETECTIVE consensus study, the surveillance strategy should be based on serial DRE (at least once yearly), PSA (at least once every six months), and repeated biopsy (no consensus on frequency, but 1-4-7 years is a commonly applied schedule).

A panel SR incorporating 263 surveillance protocols showed that 78.7% of protocols mandated per-protocol repeat biopsies within the first two years, and that 57.7% of the protocols performed repeat biopsy at least every three years for ten years after the start of AS [624].

There was clear agreement in the DETECTIVE consensus meeting, as well as in the Movember consensus group, that a PSA change alone, including PSA-doubling time (PSA-DT, < 3 years) should not change management based on its weak link with grade progression [644, 645], but rather trigger further investigation such as biopsy or repeat MRI. It was also agreed that changes on repeat MRI during AS needed a repeat biopsy before considering continuing to active treatment [620, 623].

The Movember consensus group made several recommendations that in some ways differ from the DETECTIVE consensus study, such as:

- routine DRE was not supported if MRI or other imaging was carried out routinely during AS;
- routine biopsy can be omitted if MRI combined with other parameters (PSA kinetics and density) is stable; and
- change in clinical parameters should prompt MRI with possible biopsy rather than immediate biopsy [620].

STRATCANS (STRATified CANcer Surveillance) stratifies patients into three groups based on the combination of Cambridge Prognostic Group (CPG; CPG 1 - ISUP GG1 and PSA <10 and cT1-2, CPG 2 – ISUP GG 2 or PSA 10-20 and cT1-2), PSAD (<0.15 vs. ≥0.15), and MRI visibility based on risk of progression [646]. This may be used to individualise follow-up intensities (18-12-6 months follow-up and MRI every 36-18-12 months with increasing risk, respectively, and no standard repeat biopsy in the lowest risk-tier).

6.2.1.b.6 Magnetic resonance imaging for follow-up during active surveillance

The Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) criteria were established to standardise the assessment of tumour progression on serial MRI [647]. PRECISE is a strong predictor of histological upgrading [648, 649]. Two independent meta-analyses assessed the value of MRI progression criteria for predicting histological progression (mostly defined as progression to ISUP GG ≥ 2). The pooled histological progression rate was 27% in both reviews. If biopsies were triggered only by MRI progression findings, approximately two-thirds of the biopsies would be avoided, at the cost of missing 40% of men with histological progression. In addition, at least half of biopsied men would have had negative findings for histological progression and thus would have undergone unnecessary biopsies. If histological progression were restricted to progression to ISUP GG > 3, approximately 30% of histological progression would be missed and approximately 80% of the biopsies performed would be unnecessary. The use of the PRECISE criteria did not appear to change these results [650, 651].

Another study analysed a prospectively maintained AS cohort of 369 patients (272 with ISUP GG 1 cancer and 97 with ISUP GG 2 cancer) who had been selected for AS after combined systematic and MRI-targeted sampling during confirmatory biopsy [652]. At two years, systematic biopsy, MRI-targeted biopsy and combined biopsy detected grade progression in 44 (15.9%), 73 (26.4%) and 90 patients (32.5%), respectively. This suggests that both biopsy approaches retain added value, not only for confirmatory biopsy, but also during AS [652]. Systematic biopsy cores can therefore be considered to be added to follow-up biopsy to rule out more widespread disease [226, 264, 375]. The disadvantage of overdiagnosis due to systematic cores is not present in the AS follow-up setting. Conversely, extra biopsy cores may cause discomfort and, as in the primary diagnostic setting, the risk of leaving significant PCa undetected is small and of limited relevance in a surveillance setting. As in the primary setting, the strategy of targeted/perilesional cores is therefore also recommended during AS repeat biopsy.

6.2.1.b.7 Individualised repeat biopsy during active surveillance

The basis for AS protocols includes standard repeat biopsy. However, several factors have been found to be associated with low reclassification rates and long PFS and can be used to individualise the need and frequency of AS biopsy schedules: low PSA-D [642, 653-655], low PSA velocity (PSAV) [656, 657], negative biopsy (i.e., no cancer at all) at confirmatory or repeat biopsy during AS [521, 658], and negative baseline or repeat MRI during AS [642, 653-655, 659-662]. Negative repeat biopsy during AS was associated with a 50% decrease in the risk of future reclassification and upgrading [663]. In a single-centre AS cohort of 514 patients who underwent at least three protocol-mandated biopsies after diagnosis (the confirmatory biopsy and at least two additional surveillance biopsies), men with one negative biopsy (i.e., no cancer at all) at confirmatory or second biopsy, or men with two consecutive negative biopsies had a lower likelihood of a positive third biopsy and significantly better 10-year treatment free survival [664]. Patients with stable results (PRECISE 3) on repeat MRI during AS combined with a low PSA-D (< 0.15) have a very low rate of progression and may be a group in whom standard repeat biopsy may be omitted [665].

6.2.1.b.8 *Active surveillance - change in treatment*

Patients may remain on AS whilst they have a life expectancy of > 10 years and the disease remains insignificant. A transition from AS to WW due to rising age or new comorbidity should be incorporated within conservative management strategies for PCa and in discussion with patients [666].

Histopathology criteria are the strongest reason to trigger a change in management, including. reclassification to ISUP GG ≥ 3 or detection of cribriform or intraductal growth patterns, based on systematic biopsy. The exact criteria in the targeted biopsy era remain debated. MRI-targeted biopsy induces a grade shift and ISUP GG 2–3 cancers detected by MRI-targeted biopsy have, on average, a better prognosis than those detected by means of systematic sampling. Additionally, men upgraded during AS have more favourable outcomes than men with the same ISUP GG detected at first biopsy [667]. As an increasing number of patients with favourable intermediate-risk disease are managed with AS (see Section 6.2.1.b), progression to ISUP GG 2 should not be deemed as a definitive reason to stop AS, especially when found on targeted biopsy. In addition, as acknowledged in the DETECTIVE consensus meeting, the number of positive cores is no longer an indicator of tumour volume if targeted biopsies are performed [623, 668]. Based on the findings of an SR incorporating 271 reclassification protocols, patients with low-volume ISUP GG 2 disease at recruitment and with increased systematic core positivity (> 3 cores involvement [> 50% per core]) on repeat systematic biopsies not using MRI should be reclassified [624]. As for inclusion, MRI tumour volume may be used during follow-up as a surrogate for tumour volume estimation based on systematic biopsies, though specific definitions are lacking.

6.2.1.b.9 *Psychological factors during active surveillance*

Active surveillance is the first management option in low and favourable intermediate risk PCa. A review of patient-reported considerations identified several factors influencing decision-making when considering AS. Among the identified factors were personal risk assessment, influence of family and friends, beliefs about treatment as well as doctor and system factors; underscoring the importance of individualised, relevant and clear information to support decision-making [669]. The feeling of loss of control may lead to uncertainty during AS, while re-establishing agency may restore confidence [670]. Anxiety regarding continued surveillance occurs in approximately 10% of patients on AS [671]. and was recognised as a valid reason for active treatment [231]. An alternative for patients suitable for continuing AS would be to offer psychological support to reduce the level of anxiety, as the Movember consensus group also indicated [620]. A population-based cohort study from Sweden on regional differences in AS uptake and subsequent transition to radical treatment concluded that a regional tradition of a high uptake of AS was associated with a lower probability of transition to radical treatment, but not with AS failure [672].

6.2.1.b.10 *Interventions during active surveillance*

A review of potential interventions during AS found that the use of 5-ARIs was associated with improved progression-free survival (PFS; hazard ratio: 0.59; 95% confidence interval 0.48-0.72) with limited increased toxicity [673].

A phase II RCT randomised patients to AS plus enzalutamide or AS alone. This study indicated that PSA progression could be delayed and the odds of a negative biopsy increased during the median follow-up time of 1.3 years, but patients had more side effects from the treatment without showing any long-term benefits from the treatment [674]. Evidence in support of other interventions is weak.

6.2.1.c Summary of evidence and recommendations for active surveillance strategy

Summary of evidence	LE
The oncological outcomes of low and favourable-intermediate risk PCa are very favourable, even when untreated, especially when detected during screening.	1
No modality has shown superiority over any other active management options or deferred active treatment in terms of overall and PCa-specific survival for clinically localised low/intermediate-risk disease.	1
The long-term oncological outcomes of active surveillance cohorts based on systematic prostate biopsy are very favourable.	2
The standard AS strategy should be based on PSA (at least once every six months), serial DRE (at least once yearly), and repeated biopsy.	3
Magnetic resonance imaging detects more cancers labelled with higher ISUP GG and can be used before starting AS (if not performed previously), although the impact on long-term oncological endpoints is lacking.	3

Patients with stable MRI findings have a lower risk of upgrading on repeat biopsy, allowing for de-escalation of standard repeat DRE.	2
A progression on MRI mandates a repeat biopsy to confirm histological progression before a change in treatment strategy.	3
A stable MRI (PRECISE 1-3) does not make repeat biopsy superfluous but it might be excluded in patients with low-risk tumour and a stable low PSA-D < 0.15.	2

Recommendations	Strength rating
Offer active surveillance (AS) as standard of care to all suitable patients (all low-risk disease and selected patients with favourable intermediate-risk disease).	Strong
Exclude patients with cribriform or intraductal histology on biopsy from AS.	Strong
Do not perform confirmatory biopsies if a patient has had upfront magnetic resonance imaging (MRI) and targeted and perilesional biopsies.	Weak
Perform MRI before a confirmatory biopsy if it hasn't been performed before the initial biopsy.	Strong
Take targeted and perilesional biopsy cores (of any PI-RADS ≥ 3 lesion) if a confirmatory or repeat biopsy is performed.	Strong
Perform per-protocol confirmatory prostate biopsies if MRI is not available.	Weak
Base the strategy of AS on a strict follow-up protocol including prostate-specific antigen (PSA) (at least once every six months), digital rectal examination (DRE), and repeated biopsy with or without MRI (every 2-3 years) until life expectancy falls below ten years.	Strong
Exclude patients with a low-risk PCa, a stable MRI (PRECISE 3) and a stable low PSA density (< 0.15) from repeat biopsy when MRI is repeated before repeat biopsy.	Weak
Perform MRI and repeat biopsy if PSA is rising (PSA doubling time < 3 years).	Strong
Base change in treatment on biopsy progression, not on progression on MRI, PSA, and/or DRE.	Weak

6.2.2 *Radical prostatectomy*

6.2.2.a Introduction

The goal of RP by any approach is the eradication of cancer while preserving pelvic organ function whenever possible [675]. The procedure involves removing the entire prostate with its capsule intact and SVs, followed by vesico-urethral anastomosis. The main results from multicentre RCTs involving RP are summarised in Table 6.2.3.

Table 6.2.3: Oncological results of radical prostatectomy in organ-confined disease in RCTs

Study	Acronym	Population	Treatment period	Median FU (mo.)	Risk category	CSS (%)
Bill-Axelson, *et al.* 2018 [607]	SPCG-4	Pre-PSA era	1989-1999	283	Low risk & intermediate risk	80.4 (at 23 yr.)
Wilt, *et al.* 2017 [608	PIVOT	Early years of PSA testing	1994-2002	152	Low risk & intermediate risk	95.9 91.5 (at 19.5 yr.)
Hamdy, *et al.* 2023 [593]	ProtecT	Screened population	1999-2009	180	Mainly low & intermediate risk	97 (at 15 yr.)

CSS = cancer-specific survival; FU = follow-up; mo. = months; PSA = prostate-specific antigen; yr. = years.

6.2.2.b Preoperative preparation

6.2.2.b.1 Patient education

Perioperative education has been shown to improve long-term patient satisfaction following RP [676]. Augmentation of standard verbal and written educational materials such as the use of interactive multimedia tools [677, 678] and preoperative patient-specific 3D-printed prostate models should be considered to optimise patient-centred care [679].

6.2.2.b.2 *Surgical planning*

Preoperative surgical planning is expected to assist surgeons in achieving an optimal surgical outcome. Contemporary planning involves diagnostic information combined into nomograms, in addition to imaging (e.g. mpMRI). A SR that including eight studies (one RCT, seven prospective non-randomised studies) showed that preoperative surgical planning reduced positive surgical margins regardless of whether a nomogram (RR 0.56, p = 0.009) or MRI (RR 0.72, p = 0.02) was used [680]. Incorporation of membranous urethral length according to preoperative MRI may also be useful for counselling on relative likelihood of early post-operative continence return [681].

Awareness of predisposing factors that may complicate surgery is also pivotal. In particular, higher prostate volume can increase operative complexity (but not positive surgical margins) [682], while obesity is associated with worse perioperative, oncological (positive surgical margins, RR 1.2, p < 0.01) and functional outcomes (continence, RR 1.17, p = 0.01; impotence, RR 1.08, p < 0.01) [683, 684]. Similarly, prior TURP can result in worse perioperative, oncological (positive margin rate, OR 1.25, p = 0.03) and functional (continence recovery, OR 0.60, p = 0.007; erectile function, RR 0.8, p < 0.001) outcomes [684, 685].

6.2.2.c Intraoperative considerations

6.2.2.c.1 *Nerve-sparing surgery*

Age and preoperative function are important predictors for postoperative erectile function. During RP, preservation of the neurovascular bundles (NVB) with parasympathetic nerve branches of the pelvic plexus can spare erectile function [686, 687].

A large SR and meta-analysis reported that bilateral NS resulted in improved urinary continence recovery (RR 1.08 at 12 months, p < 0.0001) across all time points with heterogeneous pooled estimates [688]. Technical factors including dissection technique, fascial dissection plane (closer the better), antegrade versus retrograde, use of thermal energy and traction and clips or low bipolar energy can be considered [689].

Patient selection for NS surgery remains challenging for clinicians, with a reliance on clinical and radiological factors, that are generally poor at predicting EPE, and consequently, the appropriateness of NS [690]. High-risk disease is not necessarily a contraindication for NS [691].

A reasonable concern is the oncological compromise and positive surgical margin rate. A 2022 SR of 18 comparative studies (no RCTs) of NS versus non-nerve-sparing RP showed a RR of side-specific positive margins of 1.5, but none of them included patients with high-risk PCa [692]. No effect of NS on BCR was seen. Follow-up was short, however, and studies were subject to selection bias with mainly low-risk patients. For those patients with high-risk PCa, side-specific NS was avoided if disease was palpable or EPE was present on MRI. Indeed, a 2019 SR showed that MRI affected the decision on whether or not to perform NS in 35% of cases without any negative impact on surgical margin rate [693].

Use of intraoperative surgical margin assessment, such as the frozen section examination (NeuroSAFE) technique, enables a systematic evaluation of surgical margins intra-operatively, allowing for adjustment if positive margins are detected to reduce positive surgical margin rates (OR 0.68; 95% 0.51-0.91 without oncological compromise according to retrospective data [694].

The multicentre prospective NeuroSAFE PROOF trial randomised 381 patients for RP with or without intraoperative margin assessment, the majority of whom were stage pT2 (64-66%) and ISUP GG 2 (76%). Higher rates of bilateral NS (82% vs. 56%) and intravesical NS (76% vs. 52%) were reported in the NeuroSAFE group. Significant improvement in patient-reported IIEF-5 scores was noted with the NeuroSAFE technique (12.7 vs. 9.7) among 344 patients at twelve months. Regarding continence, a higher ICIQ score was noted at three months (MD -1.41, p = 0.006) but not six months (MD -0.37, p = 0.46) [695]. Regarding positive surgical margins, small (≤ 3 mm) margins were higher in the NeuroSAFE group (21% vs. 13%) but large and multifocal margins were similar (14% vs. 16%). NeuroSAFE was positive in 37% of frozen sections, while tumour was present in the secondary resection in 44% of NeuroSAFE patients. At twelve months, PSA persistence or biochemical recurrence occurred in 9% of the NeuroSAFE and 6% of the control group, while freedom from recurrence or treatment at twelve months was 86% for NeuroSAFE versus 93% for standard RARP.

In summary, NS is likely to improve functional outcomes after RP such as early continence and erectile function. Nerve sparing is also more likely to result in positive surgical margins, which may influence use of salvage therapies and their associated toxicity. Surgeons should consider judicious preoperative planning and use of available resources (e.g. NeuroSAFE) to best balance optimal postoperative oncological and functional outcomes.

6.2.2.c.2 Bladder neck preservation

Whilst the majority of urinary continence is maintained by the external urethral sphincter at the membranous urethra a minor component is contributed by the internal lissosphincter at the bladder neck [696]. Preservation of the bladder neck has therefore been proposed to improve continence recovery post-RP. A RCT assessing continence recovery at twelve months and four years showed improved objective and subjective urinary continence in both the short and long term without any adverse effect on oncological outcome [697]. These findings have been confirmed by a SR [698]. However, concern remains regarding margin status for cancers located at the prostate base and caution is advised if a nearby tumour is suspected or in the presence of a large median lobe or prior TURP given their contribution to poor oncological and functional outcomes.

6.2.2.c.3 Urethral length preservation

The membranous urethra sits immediately distal to the prostatic apex and is chiefly responsible, along with its surrounding pelvic floor support structures, for urinary continence. It consists of the external rhabdosphincter, which surrounds an inner layer of smooth muscle. Preoperative MRI studies have indicated that the length of membranous urethra is variable, but very important, as every extra millimetre of membranous urethral length seen on MRI preoperatively improves early return to continence post-RP [699-701], and is a prognostic factor for regaining continence at all points until twelve months [701]. Surgeons should attempt to preserve as much urethral length as possible during RP to maximise the chance of early return to continence.

6.2.2.c.4 Vesicourethral anastomosis and reconstruction

Following prostate removal, the bladder neck is anastomosed to the membranous urethra. The objective is to create a precisely aligned, watertight, tension-free and stricture-free anastomosis that preserves the integrity of the intrinsic sphincter mechanism. Several methods have been described, based on the direct or indirect approach, the type of suture (i.e. barbed vs. non-barbed/monofilament) and variation in suturing technique (e.g. continuous vs. interrupted, or single-needle vs. double-needle running suture). Overall, although a variety of approaches, methods, and techniques are available for performing the vesicourethral anastomosis, no clear recommendations are possible due to the lack of high-certainty evidence. In practice, the chosen method should be based on surgeon experience and individual preference [702-707].

For minimally invasive (laparoscopic and robotic-assisted) RP, unidirectional barbed suture is associated with reduced anastomosis time, operative time and posterior reconstruction time versus conventional non-barbed suture during robotic-assisted radical prostatectomy (RARP) with no differences in post-operative leak rate, length of catheterisation and continence rate. However, no definitive conclusions could be drawn due to the relatively low quality of the data [703].

Effect of anterior and posterior reconstruction on continence

Prior to vesicourethral anastomosis, the effect of posterior and anterior reconstruction of surrounding support structures to return to continence has been tested in several small RCTs with conflicting results [708-712]. Four RCTs, including anterior suspension, have also shown conflicting results [713-716], where anterior suspension may result in earlier return to continence, but no long-term difference.

Variation in many aspects hampers reliable pooling of data and definitive recommendations. As there is conflicting evidence on the effect of anterior and/or posterior reconstruction on return to continence post-RP, no recommendations can be made. However, no studies showed an increase in adverse oncologic outcome or complications with reconstruction.

6.2.2.c.5 Retzius-sparing radical prostatectomy

The majority of operative approaches to both open and minimally-invasive RP involve displacement of the bladder and surrounding peritoneum away from the anterior abdominal wall and conducting of the operation in the Space of Retzius. An alternative technique is to preserve the Space of Retzius, conducting the operation from a posterior-only approach, termed “Retzius-sparing” (rsRARP). The motivations for the Retzius-sparing approach include reduced operative dissection (and possibly improved perioperative parameters) and continence outcomes. The majority of data, both from prospective series and small RCTs, indicate improved early and overall continence recovery compared to standard RARP [717, 718]. Higher positive surgical margin rates have been consistently reported for rsRARP (OR 0.45, $p < 0.05$); however, no significant differences in BCR have been reported [718, 719].

6.2.2.d Other surgical technique considerations

Management of the dorsal venous complex

Management of the dorsal venous complex will largely depend on surgical choice, as neither early (prior to) nor standard (after bladder neck incision) ligation was shown to be beneficial for functional or oncological outcomes in a single-centre RCT [720]. Ligation of the DVC can be performed with standard suture or using a vascular stapler. A single-centre RCT comparing stapler to suture ligation and suture ligation with suspension to the pubic bone reported no difference between the stapler (88%) or suture (88%) groups for continence recovery (0 pads/day with or without security pad) at three and fifteen months (99%) [721].

Removal of seminal vesicles

For oncological clearance, the seminal vesicles (SV) have traditionally been removed intact with the prostate specimen [722]. An RCT comparing nerve-sparing RP with and without an SV-sparing approach found no difference in margin status, PSA recurrence, continence or erectile function outcomes. [723]. Whilst complete SV removal should be the default, preservation of the SV tips may be considered in cases of low risk of involvement.

Bladder neck mucosal eversion

During open RP, mucosal eversion of the bladder neck aims for a mucosa-to-mucosa vesicourethral anastomosis to reduce anastomotic stricture; however, this has not been shown to reduce anastomotic stricture rate [724]. The strongest predictor of anastomotic stricture in RP is current cigarette smoking [725], but also surgical approach (open more likely than RARP) [726].

Pneumoperitoneum pressure

Use of pneumoperitoneum during minimally invasive (laparoscopic, robotic-assisted) RP is likely to reduce bleeding at the expense of increased abdominal pressure and associated physiological changes. In a randomised triple-blinded study comparing RARP (with standard DVC ligation, n=98) low-pressure (7 mmHg) versus standard-pressure (12 mmHg) pneumoperitoneum, low pressure was associated with better postoperative pain and other parameters on postoperative day one at the expense of statistically higher blood loss of questionable clinical relevance (mean 227 mL vs. 159.9mL; p = 0.001)[727].

6.2.2.e Postoperative considerations

Urinary catheter

Recommendations for use of prophylactic antibiotics at time of indwelling catheter (IDC) removal to reduce UTI are provided by the EAU Guidelines on Urological Infections. Clinicians should refer to their local institutional guidelines on thromboprophylaxis for deep venous thrombosis prophylaxis recommendations for RP.

Cystography prior to catheter removal

Cystography prior to catheter removal can check for a substantial anastomotic leak, which may defer catheter removal to allow further healing and sealing of the anastomosis. Men with LUTS, large prostates, previous TURP or bladder neck reconstruction, or intraoperative leak may benefit most from postoperative cystography as these factors have been associated with leakage [728, 729]. Heterogeneity in quality of available data, including variable prevalence of leakage and unclear long term impact, mean that recommendations on use of routine cystography cannot be provided.

Pelvic drain

A pelvic drain has traditionally been used in RP for potential drainage of urine leaking from the vesico-urethral anastomosis, blood or lymphatic fluid when a PLND has been performed. Two RCTs have been performed in the robotic-assisted laparoscopic setting [730, 731]. Patients with urine leak at intraoperative anastomosis watertight testing were excluded. Both trials showed noninferiority in complication rates when no drain was used. When the anastomosis is found to be watertight intraoperatively, it is reasonable to avoid inserting a pelvic drain. There is no evidence to guide usage of a pelvic drain in PLND.

6.2.2.f Acute and chronic complications of radical prostatectomy

An important consideration is whether complications are reduced by using newer techniques such as RARP.

Postoperative outcomes

Table 6.1.4 lists the intra- and peri- operative complications of RRP and RARP. Robot-assisted RP generally requires Trendelenberg position with head down, often using lithotomy positioning with leg stirrups. Surgeons and patients should be aware of the risk of neuropathy, affecting up to 11% of patients mostly in the lower limbs [732, 733]. An SR and meta-analysis of unplanned hospital visits and readmissions post-RP analysed 60 studies

with over 400,000 patients over a 20-year period up to 2020. The SR found an emergency room visit rate of 12% and a hospital readmission rate of 4% at 30 days postoperatively [734].

Functional outcomes

Systematic reviews have documented complication rates after RARP [735-739] and can be compared with contemporaneous reports after RRP [740]. A prospective controlled non-RCT of patients undergoing RP in 14 centres using RARP or RRP showed that, twelve months after RARP, 21.3% of patients were incontinent, as were 20.2% after RRP (adjusted OR: 1.08, 95% CI: 0.87–1.34) [741]. Erectile dysfunction was observed in 70.4% after RARP and 74.7% after RRP. The adjusted OR was 0.81 (95% CI: 0.66–0.98) [741].

An RCT comparing RARP and RRP reported outcomes at 12 weeks in 326 patients and functional outcomes at two years [742]. Urinary function scores did not differ significantly between RRP versus RARP at six and 12 weeks post-surgery (74–50 vs. 71–10, p = 0.09; 83–80 vs. 82–50, p = 0.48), with comparable outcomes for sexual function scores (30–70 vs. 32–70, p = 0.45; 35–00 vs. 38–90, p = 0.18). In the RRP group, 14 (9%) patients had postoperative complications versus six (4%) in the RARP group. A similar single-centre RCT with multiple surgeons comparing RARP to RRP in 327 patients reported lower bleeding, shorter hospitalisation duration and complications (11% vs. 17%, p = 0.1) for RARP [743]. Higher continence rates were observed for RARP at three (80% vs. 65%, p = 0.002), six (90% vs. 82%, p = 0.04) and eighteen months (95% vs. 79%, p < 0.001). Similar trends were observed for potency at three and six months.

A subsequent meta-analysis of five RCTs (1,205 patients) that compared RARP with LRP showed no difference in continence at 12 months (OR 1.95, 95% CI 0.67 – 5.62) or oncological outcomes (positive margin rate, biochemical recurrence). RARP, however, resulted in better three- (OR 1.81) and six-month (OR 1.88) continence outcomes, as well as erectile recovery in preoperatively potent patients (OR 4.05, p = 0.003) [744]. At ten years follow-up, RARP and LRP were shown to have comparable continence and potency rates, however quality of continence (totally dry) and potency (erection quality) were higher for RARP with similar oncological outcomes [745].

Recommendations for management of post-RP erectile dysfunction are provided by the EAU Guidelines on Sexual and Reproductive Health.

Table 6.2.4: Intra-and perioperative complications of retropubic RP, laparoscopic RP and RARP
(adapted from [735])

Predicted probability of event	**RARP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Bladder neck contracture	1.0	2.1	4.9
Anastomotic leak	1.0	4.4	3.3
Infection	0.8	1.1	4.8
Organ injury	0.4	2.9	0.8
Ileus	1.1	2.4	0.3
Deep vein thrombosis	0.6	0.2	1.4
Predicted rates of event	**RARP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Clavien-Dindo I	2.1	4.1	4.2
Clavien-Dindo II	3.9	7.2	17.5
Clavien-Dindo IIIa	0.5	2.3	1.8
Clavien-Dindo IIIb	0.9	3.6	2.5
Clavien-Dindo IVa	0.6	0.8	2.1
Clavien-Dindo V	< 0.1	0.2	0.2

RARP = robot-assisted radical prostatectomy; RP = radical prostatectomy; RRP = radical retropubic prostatectomy.

6.2.2.f.1 *Effect of anterior and posterior reconstruction on continence*

Preservation of integrity of the external urethral sphincter is critical for continence post-RP. Less clear is the effect of reconstruction of surrounding support structures to return to continence. Several small RCTs have been conducted, however, pooling analyses is hampered by variation in the definitions of incontinence and surgical approach, such as open versus robotic and intraperitoneal versus extra-peritoneal. In addition, techniques used to perform both anterior suspension or reconstruction and posterior reconstruction are varied. Anterior suspension, for example, is performed either through periosteum of the pubis or the combination of ligated DVC and puboprostatic ligaments (PPL). Posterior reconstruction from rhabdosphincter is described to either Denonvilliers' fascia posterior to bladder or to the posterior bladder wall itself.

Two trials assessing posterior reconstruction in RARP found no significant improvement in return to continence [708, 709]. A third trial using posterior bladder wall for reconstruction showed only an earlier return to one pad per day (median 18 vs. 30 days, p = 0.024) [710]. When combining both anterior and posterior reconstruction, where for anterior reconstruction the PPL were sutured to the anterior bladder neck, another RCT found no improvement compared to a standard anastomosis with no reconstruction [711].

Four RCTs including anterior suspension have also shown conflicting results. Anterior suspension alone through the pubic periosteum, in the setting of extra-peritoneal RARP, showed no advantage [713]. However, when combined with posterior reconstruction in RRP, one RCT showed significant improvement in return to continence at one month (7.1% vs. 26.5%, p = 0.047) and three months (15.4% vs. 45.2%, p = 0.016), but not at six months (57.9% vs. 65.4%, p = 0.609) [714]. Another anterior plus posterior reconstruction RCT using the Advanced Reconstruction of Vesico-urethral Support (ARVUS) technique and the strict definition of continence of 'no pads', showed statistically significant improvement in continence at two weeks (43.8% vs. 11.8%), four weeks (62.5% vs. 14.7%), eight weeks (68.8% vs. 20.6%), six months (75% vs. 44.1%) and twelve months (86.7% vs. 61.3%) when compared to standard posterior Rocco reconstruction [715]. Anterior suspension alone through the DVC and PPL combined without posterior construction in the setting of RARP has shown improvement in continence at one month (20% vs. 53%, p = 0.029), three months (47% vs. 73%, p = 0.034) and six months (83% vs. 100%, p = 0.02), but not at twelve months (97% vs. 100%, p = 0.313) [716]. Together, these results suggest a possible earlier return to continence, but no long-term difference.

A novel method of urethral reconstruction with peritoneal support flaps was shown in a randomised trial compared to standard RARP (n = 96) to improve urinary continence recovery (0-1 pad) at one month (73% vs. 49%, p = 0.017) and three months (93% vs. 77%, p = 0.025); however, patient reported outcomes, complications and oncological outcomes were similar [712].

Because there is conflicting evidence regarding the effect of anterior and/or posterior reconstruction on return to continence post-RP, no recommendations can be made. However, no studies showed an increase in adverse oncologic outcome or complications with reconstruction.

6.2.2.f.2 *Deep venous thrombosis prophylaxis*

As with all pelvic cancer surgery lasting over one hour, there is a measurable increased risk of deep vein thrombosis, and therefore consideration should be given to chemical thrombosis prophylaxis, commonly used for three to four weeks after surgery. This should be adapted based on national recommendations, when available.

6.2.3 *Radiotherapy*

Intensity-modulated RT (IMRT) or volumetric-modulated arc therapy (VMAT) with image-guided RT (IGRT) is currently widely recognised as the standard treatment approach for EBRT.

6.2.3.a External beam radiation therapy

6.2.3.a.1 *Technical aspects*

Intensity-modulated RT and VMAT employ dynamic multi-leaf collimators, which automatically and continuously adapt to the contours of the target volume seen by each beam. Viani *et al.* show significantly reduced acute and late grade ≥ 2 genitourinary (GU) and gastrointestinal (GI) toxicity in favour of IMRT, while BCR-free rates did not differ significantly when comparing IMRT with three-dimensional conformal RT (3D-CRT) in an RCT comprising 215 patients [746]. A meta-analysis by Yu *et al.* (23 studies, 9,556 patients) concluded that IMRT significantly decreases the occurrence of grade 2–4 acute GI toxicity, late GI toxicity and late rectal bleeding, and achieves better PSA relapse-free survival in comparison with 3D-CRT. Intensity-modulated EBRT and 3D-CRT show comparable acute rectal toxicity, late GU toxicity and OS, while IMRT slightly increases the morbidity of acute GU toxicity [747]. Therefore, IMRT plus IGRT remain the SOC for the treatment of PCa.

The advantage of VMAT over IMRT is shorter treatment times, generally two to three minutes in total. Both techniques allow for a more complex distribution of the dose to be delivered and provide concave isodose curves, which are particularly useful as a means of sparing the rectum. Radiotherapy treatment planning for IMRT and VMAT differs from that used in conventional EBRT, requiring a computer system capable of 'inverse planning' and the appropriate physics expertise. Treatment plans must conform to prespecified dose constraints to critical organs at risk of normal tissue damage and a formal quality assurance process should be routine.

With dose escalation using IMRT/VMAT, organ movement becomes a critical issue in terms of both tumour control and treatment toxicity. Techniques will therefore combine IMRT/VMAT with some form of IGRT (usually gold-marker or cone-beam CT), in which organ movement can be visualised and corrected for in real time, although the optimum means (number of applications per week) of achieving this is still unclear [748, 749]. Tomotherapy is another technique for the delivery of IMRT, using a linear accelerator mounted on a ring gantry that rotates as the patient is delivered through the centre of the ring in a manner analogous to spiral CT scanning.

The use of MR-guided adapted RT is still investigational [750]. Planning studies confirm that MR-based adaptive RT significantly reduces doses to organs at risk (OAR), and this may translate into clinical benefit [751]. Although the rates of acute GI and GU toxicity appear low - based mostly on patients treated with stereotactic RT [752], follow-up is too short for definitive conclusions [750]. Due to the daily fraction time of up to 45 minutes [750, 752], the heavy MR-workflow and the limited field size (rendering most pelvic fields too large), MR-guided adapted RT implementation is not yet routine [750]. A prospective single centre RCT, the MIRAGE trial (CT-guided Stereotactic Body Radiation Therapy and MRI-guided Stereotactic Body Radiation Therapy for Prostate Cancer) demonstrates reduced acute GU and GI toxicity with MRI-guided SBRT and margin reduction from 4mm to 2mm [753]. Secondary endpoints of cumulative incidence rates of late grade ≥ 2 toxicity at two years with MRI-guided versus CT-guided SBRT were 27% (95% CI 19–39%)] versus 51% (95% CI 41–63%) for GU toxicity (p = 0.004), and 1.4% (95% CI 0.2–9.6) versus 9.5% (95% CI 4.6–19) for GI toxicity (p = 0.025). Cumulative logistic regression revealed that MRI-guided SBRT was associated with significantly lower odds of a clinically relevant deterioration in bowel function according to the Expanded Prostate Cancer Index Composite-26 score (OD 0.444, 95% CI 0.209–0.942; p = 0.035) and in the Sexual Health Inventory in Men score (OD 0.366, 95% CI 0.148–0.906; p = 0.03) [754].

6.2.3.a.2 ***Dose escalation***

Local control is a critical issue for the outcome of RT of PCa. Local failure due to insufficient total dose has been shown to be prognostic for death from PCa, because a second wave of metastases is seen five to ten years later [755]. Several RCTs have shown that dose escalation (range 74–80Gy) has a significant impact on 10-year biochemical relapse as well as metastases and disease-specific mortality [756-763]. These trials have generally included patients from several risk groups, and the use of neoadjuvant/adjuvant ADT has varied (see Table 6.2.5). The best evidence of an OS benefit in patients with intermediate- or high-risk PCa derives from a non-randomised, but well-conducted propensity-matched retrospective analysis of the United States National Cancer Database by Kalbasi *et al.*, including a total of 42,481 patients [764]. If IMRT/VMAT and IGRT are used for dose escalation, rates of severe late side effects (> grade 3) are 2–4% for the rectum and 2–6% for the GU tract [758, 765].

The concept of a focal boost to the dominant intraprostatic lesion (DIL) visible on MRI rather than global prostate dose escalation has been successfully validated in a RCT of 571 intermediate- and high-risk patients [765, 766]. Patients were randomised between 77Gy in 35 fractions of 2.2Gy and the same dose plus a focal boost up to 18Gy. Additional ADT was given to 65% of patients in both arms, however, the duration of the ADT was not reported. With a median follow-up of 106 months, there was a significant improvement of ten-year biochemical DFS (BDFS) (primary endpoint) from 71% (95%CI 65-77%) in the control arm to 86% (95%CI 81-91%) in the focal boost arm (p < 0.001). In addition, focal boosting decreased local and regional lymph node failure but did not impact DMFS and OS. No significant difference for late GU or GI toxicity grade ≥ 2 (23% and 12% vs. 28% and 13%) was documented at up to five years [765]. For grade ≥ 3 GU-toxicity, these numbers were 3.5% and 5.6% (p > 0.05). However, longer follow-up is needed to assess late GU toxicity [767]. Of note, there was a dose response, with increased boost dose associated with reduced distant metastatic failure [766]. Systematic review of MRI-defined DIL focal boost studies using standard fractionation shows good tolerability and improved BPFS [768]. Its role when using hypofractionation and ultrahypofractionation is under investigation.

6.2.3.a.3 *Hypofractionation*

Fractionated RT utilises differences in the DNA repair capacity of normal and tumour tissue and slowly proliferating cells are very sensitive to an increased dose per fraction [769]. A meta-analysis of 25 studies including > 14,000 patients concluded that, since PCa has a slow proliferation rate, hypofractionated RT could be more effective than conventional fractions of 1.8–2Gy [770]. Hypofractionation (HFX) has the added advantage of being more convenient for the patient at lower cost.

Moderate HFX is defined as RT with 2.5–3.4Gy/fx. Several studies report on moderate HFX applied in various techniques, including in part ADT [771-778]. A Cochrane review on moderate HFX for clinically localised PCa [779] included eleven studies (n = 8,278) with a median follow-up of 72 months showing little or no difference in PCa-specific survival (HR: 1.00) when compared to conventionally fractionated radiotherapy. Based on four studies (n = 3,848), moderate HFX to the prostate alone likely makes little or no difference to late radiation GU toxicity (RR: 1.05) or GI toxicity (RR: 1.1). An individual patient meta-analysis of seven phase III clinical trials comparing conventional with iso-toxic or dose escalated moderate HFX, shows no differences in PFS (HR 0.92, 95% CI 0.81–1.05; p = 0.21 and 0.94, 0.82–1.09; p = 0.43, respectively) [780]. The odds of grade 2 or higher gastrointestinal toxic effects were significantly higher with dose-escalated (OR 1·48, 95% CI 1·14–1·92; p=0·0035) with bowel quality-of-life decrement (OR 1·68, 95% CI 1·07–2·61; p=0·023). Dose escalated moderate HFX is therefore not recommended.

Toxicity outcomes in two RCTs recruiting high-risk patients and adding elective pelvic nodal radiation have reported. The PCS-5 multicentre RCT recruited high risk patients (25.9% T3-4) and an initial two-year toxicity analysis demonstrated comparable G2+ GI toxicity across treatment arms with lower rates of late G2+ GU toxicity with HFX [781]. No differences were seen in survival outcomes at median follow-up of five years although, as secondary endpoints, extrapolation of survival results is limited by small sample size [782]. In the single-center randomised pHART2-RCT, an increase in five-year G3+ GI toxicity was noted when HFX was combined with elective pelvic nodal RT [783]. In the postoperative setting, moderate HFX is non-inferior in terms of two-year patient-reported toxicity to conventional fractionation with similar rates of patient reported GI and GU toxicity [784].

Ultra-HFX uses even larger doses per fraction and requires IGRT or ideally stereotactic body RT (SBRT). Table 6.2.7 provides an overview of selected studies investigating the role of Ultra-HFX in treating predominantly intermediate-risk localised disease. Biochemical control is comparable to conventional fractionation. However, there are concerns about higher-grade GU toxicity, and UHFX should be avoided in patients with severe pre-existing lower urinary tract symptoms (IPSS > 19) and/or outflow obstruction with or without median lobe [785, 786]. In the HYPO-RT-PC randomised trial (n = 1,200), no difference in failure-free survival was seen for conventional or ultra-HFX, but acute grade ≥ 2 GU toxicity was 23% versus 28% (p = 0.057), favouring conventional fractionation. There were no significant differences in long-term toxicity [785]. Presentation reports indicate that after a median follow-up duration of 10.6 years, UHF was shown to be non-inferior to CF in terms of failure-free survival, with ten-year failure-free survival rates of 72% for UHF compared with 65% for CF (adjusted HR = 0.84, 95% CI: 0.69-1.03) [787].

In the Intensity-modulated fractionated RT versus SBRT for PCa (PACE-B) trial, acute grade ≥ 2 GU or GI toxicities did not differ significantly between conventional fractionation and ultra-HFX [788]. At two years, treatment was well-tolerated in both arms with no differences in RTOG ≥ grade 2 GU or GI toxicities, but clinician scoring of urinary toxicity using CTCAE and patient-reported Expanded Prostate Cancer Index Composite (EPIC)-26 urinary bother scores were both higher in the SBRT arm [789]. After 74 months median follow-up, five-year biochemical/clinical failure free-rates were 94.6% (95% CI 91.9%, 96.4%) in the control arm and 95.8% (95% CI 93.3%, 97.4%) in the SBRT arm, confirming that SBRT is non-inferior (HR 0.73 90% CI 0.48-1.12, p for non-inferiority = 0.004). The cumulative five-year rate of late RTOG grade 2+ GI toxicity was similar in both arms (10%), but higher rates of cumulative five-year RTOG grade 2+ GU toxicity occurred with SBRT at 26.9% (95% CI 22.8, 31.5%) compared to the control arm at 18.3% (95% CI 14.8, 22.5%) [786]. The GU toxicity is temporary with no statistical difference in clinician-reported toxicity between groups at five years and no clinically relevant difference in patient-reported outcomes in the five years of follow-up. Adopting planning dose constraints to the penile bulb might minimise ED, particularly in younger patients [790].

6.2.3.a.4 *Neoadjuvant or adjuvant hormone therapy plus radiotherapy*

The combination of RT with luteinising hormone releasing hormone (LHRH) ADT has superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III RCTs [791-802] (Table 6.2.8). The main message is that, for intermediate-risk disease, a short duration of four to six months is optimal, while a longer duration of two to three years is needed for high-risk patients. The largest RCT in intermediate-risk disease

comparing dose-escalated RT with or without six months of ADT failed to demonstrate an OS advantage with a median follow-up time of 6.3 years. Six months of ADT use was associated with reduced PSA failure, fewer distant metastases and improved prostate-cancer-specific mortality [802].

The question of the added value of EBRT combined with ADT has been clarified by three RCTs. All showed a clear benefit of adding EBRT to long-term ADT (Table 6.2.9).

The combination of ADT with various forms of RT has been studied extensively, with extremely strong evidence for the use of such combined modality therapy in several settings. The MARCAP (Individual Patient Data Meta- Analysis of Randomised Trials in Cancer of the Prostate) consortium conducted a meta-analysis of trials using individual patient data (IPD) and a primary endpoint of MFS. Trials were eligible if they studied the use or prolongation of ADT in patients receiving definitive RT and included 12 trials with 10,853 patients. Median follow-up was over 11 years. The use of ADT was clearly associated with significant improvements in BCR, metastatic recurrence, MFS and OS. The benefits of ADT were independent of RT dose, age and risk groups comparing NCCN unfavourable intermediate-risk, high-risk and locally advanced disease. The extension of duration of neoadjuvant ADT showed no demonstrable benefits [803].

A meta-analysis from two RCTs (RTOG 9413 and Ottawa 0101) compared neoadjuvant/concomitant versus adjuvant ADT (without substratifying between favourable and unfavourable intermediate-risk disease) in conjunction with prostate RT and reported superior PFS with adjuvant ADT, but the data heterogeneity means that this observation is hypothesis-generating only [804].

In addition, a Canadian two-arm dose-escalated (76Gy) RCT compared neoadjuvant and concomitant with adjuvant short-term ADT in 432 patients with intermediate-risk PCa. After ten years, no significant difference in OS or RT-related grade ≥ 3 GI or GU toxicity was seen [805]. Therefore, both regimens in combination with dose escalation are reasonable standards.

6.2.3.b Proton beam therapy

In theory, proton beams are an attractive alternative to photon-beam RT for PCa, because they deposit almost all their radiation dose at the end of the particle's path in tissue (the Bragg peak) in contrast to photons, which deposit radiation along their path. There is also a very sharp fall-off for proton beams beyond their deposition depth, meaning that critical normal tissues beyond this depth could be effectively spared. In contrast, photon beams continue to deposit energy until they leave the body, including an exit dose. The PARTIQoL Phase III RCT compared proton beam therapy (PBT) with IMRT in 450 participants with localised prostate cancer. With a median follow-up of 60.3 months, no difference in any QoL domain or PFS was found [806]. Proton beam therapy has no advantages over less resource-intensive IMRT/VMAT. However, the publication of the full study is awaited to confirm the results.

Table 6.2.5: Randomised trials of dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
MD Anderson study 2011 [763]	301	T1-T3, N0, M0, PSA ≤ 10ng/mL PSA 10-20ng/mL PSA > 20ng/mL	70 vs.78Gy	15 yr.	DM, DSM, FFF	All patients: 18.9% FFF at 70Gy; 12% FFF at 78Gy; (p = 0.042) 3.4% DM at 70Gy; 1.1% DM at 78Gy; (p = 0.018) 6.2% DSM at 70Gy; 3.2% DSM at 78Gy; (p = 0.043) No difference in OS (p > 0.05)

PROG 95-09 2010 [757]	393	T1b-T2b, PSA ≤ 15ng/mL 75% low-risk pts. Low risk: T1-2a, PSA < 10mg/mL, GS ≤ 6. Interim risk: PSA 10-15ng/mL or GS 7 or T2b. High risk: GS 8-10.	70.2 vs.79.2Gy, including proton boost 19.8 vs. 28.8Gy	8.9 yr.	10-yr. ASTRO BCF	All patients: 32% BF at 70.2Gy; 17% BF at 79.2Gy; (p < 0.0001) Low-risk patients: 28% BF at 70.2Gy; 7% BF at 79.2Gy; (p < 0.0001)
MRC RT01 2014 [762]	843	T1b-T3a, N0, M0 PSA < 50ng/mL neoadjuvant ADT	64 vs. 74Gy	10 yr.	BFS, OS	43% BFS at 64Gy; 55% BFS at 74Gy; (p = 0.0003) 71% OS both groups (p = 0.96)
Dutch RCT 2014 [761]	664	T1b-T4 143 pts. with (neo) adjuvant ADT	68 vs. 78Gy	110 mo.	Freedom biochemical (Phoenix) and/or clinical failure at 10 yr.	43% FFF at 68Gy; 49% FFF at 78Gy; (p = 0.045)
GETUG 06 2011 [760]	306	T1b-T3a, N0, M0 PSA < 50ng/mL	70 vs. 80Gy	61 mo.	BCF (ASTRO)	39% BF at 70Gy; 28% BF at 80Gy
RTOG 0126 2018 [756]	1,532	T1b-T2b ISUP GG 1 + PSA 10-20ng/mL or ISUP GG 2/3 + PSA < 15ng/mL	70.2 vs. 79.2Gy	100 mo.	OS, DM, BCF (ASTRO)	75% OS at 70.2Gy; 76% OS at 79.2Gy 6% DM at 70.2Gy; 4% DM at 79.2Gy; (p = 0.05) 47% BCF at 70.2Gy; 31% BCF at 79.2Gy; (p < 0.001; Phoenix, p < 0.001)
FLAME Trial [765-767]	571	EAU risk classification: Intermediate risk (15%) High risk (84%)	77Gy (35fx 2.2Gy) vs. 77Gy 35fx) + focal boost (up to 18Gy) ADT (65% both arms - duration unknown)	106 mo.	bDFS (10 yr.)	bDFS 86% at 77Gy+boost; 71% at 77Gy (p<0.001) Focal boost in favour of local and regional lymph node DFS

ADT = androgen-deprivation therapy; BCF = biochemical failure; BFS = biochemical progression-free survival; DM = distant metastases; DSM = 50 disease-specific mortality; FFF = freedom from biochemical or clinical failure; fx = fractions; GS = Gleason score; ISUP = International Society of Urological Pathology; MFS = metastasis-free survival; mo. = months; n = number of patients; OS = overall survival; PSA = prostate-specific antigen; bDFS = biochemical disease-free survival; yr. = years.

Table 6.2.6: Major phase III randomised trials of moderate hypofractionation for primary treatment

Study/ Author	n	Risk, ISUP GG, or NCCN	ADT	RT Regimen	BED, Gy	Follow-up (median)	Outcome
Lee, *et al.* 2024 [807]	550 542	low risk	None	70Gy/28fx 73.8Gy/41fx	80 69.6	150 mo.	12 yr. DFS 56.1% (95% CI, 51.5 to 60.5) control arm and 61.8% (95% CI, 57.2 to 66.0) for HFX. HR 0.85 (95% CI, 0.71 to 1.03)
Dearnaley, *et al.* CHHiP 2016 [774]	1,077/19fx 1,074/20fx 1,065/37fx	15% low 73% intermediate 12% high	3-6 mo. before and during EBRT	57 Gy/19fx 60 Gy/20fx 74 Gy/37fx	73.3 77.1 74	62 mo.	5 yr. BCDF 85.9% (19fx) 90.6% (20fx) 88.3% (37fx)
De Vries, *et al.* 2020 [808]	403 392	30% ISUP GG 1 45% ISUP GG 2-3, 25% ISUP GG 4-5	None	64.6 Gy/19fx 78 Gy/39fx	90.4 78	89 mo.	8-yr. OS 80.8% vs. 77.6% (p = 0.17) 8 yr. TF 24.4% vs. 26.3%
Catton, *et al.* 2017 [776]	608	Intermediate risk 53% T1c 46% T2a-c	None	60 Gy/20fx	77.1	72 mo.	5 yr. BCDF both arms 85% HR: 0.96 (n.s.)
	598	9% ISUP GG 1 63% ISUP GG 2 28% ISUP GG 3		78Gy/39fx	78		
Glicksman, *et al.* 2024 PHART-2 [783]	186	All high risk N0M0 T1-2 82.8% T3-4 12.2%	22 mo. median	68Gy to prostate (SIB) + 48Gy to pelvis in 25fx 78Gy to prostate + 46Gy to pelvis in 39fx	82 78	67 mo.	No difference in acute toxicity and PROs Higher 5-yr cumulative G3+ GI in HFX 13.5% (95% CI, 7.1%-21.9%) vs 2.4% (95% CI, 0.5%-7.6%) (P = 0.01)
Niazi, *et al.* 2023 PCS-5 [781]	329	All high risk N0M0 T1-2 73.8% T3-4 25.9%	28 mo. - 3 mo. before during and after EBRT	68Gy to prostate (SIB) + 45Gy to pelvis in 25fx 76Gy to prostate + 46Gy to pelvis in 38fx	82 76	24 mo.	Similar 2 yr. G2+ GI toxicity (8-10%) Reduced 2 yr G2+ GU toxicity with HFX (4.3% vs 15.9%; p=0.035)

ADT = androgen deprivation therapy; BCDF = biochemical or clinical disease failure; BED = biologically equivalent dose, calculated to be equivalent in 2Gy fractions using an α/ß of 1.5Gy; DFS = disease-free survival; EBRT = external beam radiotherapy; fx = fractions; GG = grade group; GI = gastrointestinal; GU = genitourinary; HFX = hypofractionation; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo. = months; n = number of patients; OS = overall survival; NCCN = National Comprehensive Cancer Network; n.s. = not significant; PROs = patient-reported outcomes; RT = radiotherapy; SIB = simultaneous integrated boost; TF = treatment failure; yr. = years.

Table 6.2.7: Selected trials on ultra-hypofractionation for intact localised PCa

Study	n	med FU (mo)	Risk-Group	Regimen (TD/fx)	Outcome
Widmark *et al.* 2019 HYPO-RT-PC [785]	1,200	60	89% intermediate 11% high	78 Gy / 39 fx, 8 wks 42.7 Gy / 7 fx, 2.5 wks No SBRT	FFS at 5 yrs 84% in both arms
Brand *et al.* 2019 Tree *et al.* 2022 Van As *et al.* 2024 [789] PACE-B [788] [786]	874	74	9.3% NCCN low 90.7% NCCN intermediate ISUP GG 3 excluded	78Gy/39fx, 7.5 wks or 62Gy/20fx 4wks 36.25Gy/5fx, 1-2 wks SBRT	Biochemical/clinical FFS at 5 yrs 94.6% (CRT) vs. 95.6% (SBRT) Cumulative 5-yr G 2+ GI toxicity similar (10%) Cumulative 5-yr G2+ GU SBRT 26.9% (95%CI 22.8,31.5%) CRT 18.3% (95%CI 14.8,22.5%).

CRT = control arm radiotherapy; FFS = failure-free survival; FU = follow-up; fx = number fractions; mo. = months; n = number of patients; SBRT = stereotactic body radiotherapy; TD = total dose; wks = weeks; yr. = years.

Table 6.2.8: Selected studies of use and duration of ADT in combination with RT for PCa

Study	TNM stage	n	Trial	ADT	RT	Effect on OS
RTOG 85-31 2005 [793]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65-70Gy	Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with ISUP grade group 2-5
RTOG 94-13 2007 [797]	T1c-4 N0-1 M0	1,292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)
RTOG 86-10 2008 [794]	T2-4 N0-1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65-70Gy RT	No significant difference at 10 yr.
D'Amico AV, *et al.* 2008 [795]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70Gy 3D-CRT	Significant benefit that may pertain only to men with no or minimal co-morbidity (HR: 0.55, 95% CI: 0.34-0.90, p = 0.01)
RTOG 92-02 2008 [798]	T2c-4 N0-1 M0	1,554	Short vs. prolonged ADT	LHRH agonist given for 2 yr. as adjuvant after 4 mo. as neoadjuvant	65-70Gy	p = 0.73, p = 0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with ISUP grade group 4-5

EORTC 22961 2009 [799]	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr.	70Gy 3D-CRT	Better result with 3 yr. treatment than with 6 mo. (3.8% improvement in survival at 5 yr.)
EORTC 22863 2010 [792]	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRH agonist for 3 yr. (adjuvant)	70Gy RT	Significant benefit at 10 yr. for combined treatment (HR: 0.60, 95% CI: 0.45-0.80, p = 0.0004).
TROG 96-01 2011 [796]	T2b-4 N0 M0	802	Neoadjuvant ADT Duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66Gy 3D-CRT	No significant difference in OS reported; benefit in PCa-specific survival (HR: 0.56, 95% CI: 0.32-0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65-1.08, p = 0.18)
RTOG 99-10 2015 [800]	intermediate risk 94% T1-T2; 6% T3-4	1,579	Short vs. prolonged ADT	LHRH agonist 8 + 8 vs. 8 + 28 wk.	70.2Gy 2D/3D	67 vs. 68%, p = 0.62, confirms 8 + 8 wk. LHRH as a standard
PCSIII 2020 [801]	Intermediate risk	600	76Gy alone vs. 76Gy + ADT vs. 70Gy + ADT	LHRH + bicalutamide 6 mo. 4 mo. prior to RT	70 vs. 7 Gy	Significantly improved biochemical failure-free and PCa-specific survival for ADT arms, with no difference in OS.
RTOG 0815 2023 [802]	Intermediate risk	1,492	Dose - escalated RT ± ADT	LHRH agonist/ antagonist + bicalutamide or flutamide 6 mo. 2 mo. prior to RT	79.2Gy (89%) 45Gy + BT boost (11%)	No difference in OS. Significantly improved biochemical failure-free, metastatic-free survival and PCa-specific survival for ADT arm.

3D-CRT = three-dimensional conformal radiotherapy; ADT = androgen deprivation therapy; BT = brachytherapy; CI = confidence interval; EBRT = external beam radiotherapy in standard fractionation; HR = hazard ratio; ISUP = International Society of Urological Pathology; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; RP = radical prostatectomy; RT = radiotherapy; wks = weeks; yr. = years.

Table 6.2.9: Selected studies of ADT in combination with, or without, RT for PCa

Study	TNM stage	n	Trial design	ADT	RT	Effect on OS
SPCG-7/ SFUO-3 2016 [809]	T1b-2 WHO Grade 1-3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo. Plus continuous flutamide	70Gy 3D-CRT vs. no RT	34% (95% CI: 29-39%) vs. 17% (95% CI: 13-22% CSM at 12 (15) yr. favouring combined treatment (p < 0.0001 for 15-yr. results) NCIC CTG PR.3/ MRC
PRO7/NCIC 2015 [810]	T3-4 (88%), PSA > 20ng/mL (64%), ISUP GG 4-5 (36%) N0 M0	1,205	ADT ± EBRT	Continuous LHRH agonist	65-70Gy 3D-CRT vs. no RT	10-yr. OS = 49% vs. 55% favouring combined treatment HR: 0.7, p < 0.001)
Sargos, *et al.*, 2020 [811]	T3-4 N0 M0	273	ADT ± EBRT	LHRH agonist for 3 yr.	70Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5-yr. OS 71.4% vs. 71.5%

3D-CRT = three-dimensional conformal radiotherapy; ADT = androgen-deprivation therapy; CSM = cancer-specific mortality; EBRT = external beam radiotherapy; HR = hazard ratio; LHRH = luteinising hormone-releasing hormone; mo. = months; n = number of patients; OS = overall survival; PSA = prostate-specific antigen; RT = radiotherapy; yr. = years.

6.2.3.c Spacer during external beam radiation therapy

Biodegradable spacer insertion involves using a liquid gel or balloon to increase the distance between the prostate and rectum and consequently reduce the amount of radiation reaching the rectum. Various materials have been used with most evidence available for CE-marked hydrogel spacers [812]. An SR and meta-analysis including three RCTs, three prospective cohorts, and eleven retrospective cohort studies demonstrated that the use of spacer is associated with lower acute grade 2+ rectal toxicity (3.07% vs. 6.05%, RR=0.53, 95% CI=0.33–0.86, p < 0.001) and late grade 2+ rectal toxicity (1.62% vs. 9.35%, RR: 0.25, 95% CI: 0.15–0.42,p < 0.001). No difference is observed in significant grade 3+ GI (acute or late) events and there is no statistical difference in bowel-related QoL (risk difference= −0.16, 95% CI: −0.38–0.06, p = 0.15) [813]. With more widespread clinical use safety reports have described uncommon, but severe and life changing complications including prostatic abscess, fistulae and sepsis. Implantation is associated with a learning curve and should only be undertaken by teams with experience of TRUS and transperineal procedures with robust audit reporting in place [814].

6.2.3.d Brachytherapy

6.2.3.d.1 Low-dose rate brachytherapy

Low-dose rate (LDR) BT uses radioactive seeds permanently implanted into the prostate. Low-dose rate monotherapy [815] can be offered to patients with NCCN-favourable intermediate risk and good urinary function defined as an International Prostatic Symptom Score (IPSS) < 12 and maximum flow rate > 15mL/min on urinary flow tests [816]. The RTOG phase III RCT compared LDR BT +/- EBRT in participants with ISUP GG1 and PSA < 20 or ISUP GG 2 and PSA < 10 and found that the addition of EBRT resulted in increased toxicity but no improvement in freedom from progression [817].

Patients having had a previous TURP can undergo BT without an increase in risk of urinary toxicity with due attention to dose distribution. A minimal channel TURP is recommended, leaving at least 1 cm rim of prostate tissue around the post-TURP urethral defect at the posterolateral sides of the prostate and there should be at least a 3-month interval between TURP and BT to allow for adequate healing [818-821].

The only available RCT comparing RP and LDR BT as monotherapy was closed due to poor accrual [822]. Outcome data are available from several large population cohorts with mature follow-up [823-827]. A significant correlation has been shown between the implanted dose and biochemical control [828]. A D90 (dose covering 90% of the prostate volume) of > 140Gy leads to a significantly higher biochemical control rate (PSA < 1.0ng/mL) after four years (92 vs. 68%). There is no OS benefit in adding neoadjuvant or adjuvant ADT to LDR monotherapy [829].

Low-dose-rate BT can be combined with EBRT in NCCN-unfavourable intermediate-risk PCa and high-risk patients. External beam RT (total dose of 78Gy) has been compared with EBRT (total dose 46Gy) followed by LDR BT boost (prescribed dose 115Gy) in intermediate-risk and high-risk patients in the ASCENDE-RT randomised trial with twelve months of ADT in both arms [830, 831]. The LDR boost resulted in 5-, 7- and 10-year PSA PFS increase (89%, 86% and 85%, respectively, compared to 84%, 75%, 70%) but with no impact on distant metastasis or OS. This improvement in biochemical control was achieved at a cost of increased late grade 3+ GU toxicity (18% compared to 8%) and two treatment-related deaths [831, 832]. Urinary toxicity was mainly in the development of urethral strictures and incontinence, and great care should be taken during treatment planning.

6.2.3.d.2 High-dose rate brachytherapy

High dose rate (HDR) BT uses a radioactive source temporarily introduced into the prostate to deliver radiation. Table 6.2.10 outlines the technical differences. The use of the GEC (Groupe European de Curietherapie)/ESTRO Guidelines is strongly recommended [833]. High-dose-rate BT can be delivered in single or multiple fractions and is often combined with EBRT of at least 45Gy, conventionally fractionated [834]. A retrospective analysis on 1,641 intermediate- and high-risk patients demonstrated a better distant-metastasis free survival when a HDR BT boost was added to 50–54Gy EBRT. The difference mounted to 12% at ten years [835]. An SR of non-RCTs and data from population studies suggest outcomes with EBRT plus HDR BT are superior to EBRT alone [836, 837].

A single-centre RCT of EBRT (55Gy in 20 fractions) vs. EBRT (35.75Gy in 13 fractions), followed by HDR BT (17Gy in two fractions over 24 hours) has been reported [838]. In 218 patients with T1–3 N0M0 PCa, the combination of EBRT and HDR BT showed a significant improvement in the biochemical disease-free rate (p = 0.04) at five and ten years (75% and 46% compared to 61% and 39%). However, an unexpectedly high rate of early recurrences was observed in the EBRT arm alone, even after two years, possibly due to a dose lower than the current standard used [838].

Supporting, but not definitive, evidence of the benefit of HDR boost is available from the TROG 03.04 RADAR trial. This multi-centre study had upfront radiation dose escalation (non-randomised) with dosing options of 66, 70 or 74Gy EBRT, or 46Gy EBRT plus HDR BT boost and randomised men with locally advanced PCa to 6- or 18-months ADT. After a minimum follow-up of ten years, HDR boost significantly reduced distant progression, the study primary endpoint (HR: 0.68, 95% CI: 0.57–0.80; $p < 0.0001$), when compared to EBRT alone and, independent of duration of ADT, HDR boost was associated with increased IPSS of three points at 18 months post-treatment resolving by three years but decreased rectal symptoms when compared to EBRT [839]. Although radiation dose escalation using BT boost provides much higher biological doses, the TROG 03.04 RADAR RCT and SRs show ADT use independently predicts better outcomes regardless of radiation dose intensification [829, 839, 840]. Omitting ADT may result in inferior OS and based on current evidence ADT use and duration should be in line with that used when delivering EBRT alone.

Fractionated HDR BT as monotherapy can be offered to patients with intermediate-risk PCa, who should be informed that results are only available from limited series in very experienced centres. Five-year PSA control rates of 93.5% for intermediate-risk PCa are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [841]. Single fraction HDR monotherapy should not be used as it has inferior biochemical control rates compared to fractionated HDR monotherapy with local failure rates at eight years of 35.9% versus 11.2% ($p<0.001$) [842].

Table 6.2.10: Difference between LDR and HDR brachytherapy

	Differences in prostate brachytherapy techniques
Low dose rate (LDR)	Permanent seeds implanted
	Uses Iodine-125 (I-125) (most common)
	Palladium-103 (103Pd-) or Cesium-131 isotopes
	Radiation dose delivered over weeks and months
	Acute side effects resolve over months
	Radiation protection issues for patient and carers
High dose rate (HDR)	Temporary implantation
	Iridium-192 (IR-192) isotope introduced through implanted needles or catheters
	Radiation dose delivered in minutes
	Acute side effects resolve over weeks
	No radiation protection issues for patient or carers

6.2.3.e Acute side effects of external beam radiotherapy and brachytherapy

Gastrointestinal and urinary side effects are common during and after EBRT. In the EORTC 22991 trial, approximately 50% of patients reported acute GU toxicity of grade 1, 20% grade 2, and 2% of grade 3. In the same trial, approximately 30% of patients reported acute grade 1 GI toxicity, 10% grade 2, and less than 1% grade 3. Common toxicities included dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis [843]. In addition, general side effects such as fatigue are common. It should be noted that the incidence of acute side effects is greater than that of late effects, implying that most acute effects resolve.

In an RCT comparing patient reported QoL after LDR or HDR boost combined with external beam radiotherapy to the pelvis, more intense and prolonged acute urinary side effects are noted with LDR boost [844]. In an RCT of conventional-dose EBRT vs. EBRT and LDR BT, the incidence of acute proctitis was reduced in the BT arm, but other acute toxicities were equivalent [830]. In a pooled analysis of 864 patients treated using extreme HFX and stereotactic RT, declines in urinary and bowel domains were noted at three months which returned to baseline - or better - by six months [845].

6.2.4 Investigational therapies

6.2.4.a Background

In addition to RP, EBRT and BT, other modalities have emerged as potential therapeutic options in patients with clinically localised PCa [846-848]. These new modalities have been developed as minimally invasive procedures with the aim of providing equivalent oncological safety, reduced toxicity and improved functional outcomes.

In this section, both whole-gland and focal treatment [849, 850] will be considered, looking particularly at high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy), focal photodynamic therapy (PDT), and irreversible electroporation (IRE), as sufficient data are available to form the basis of some initial judgements. Other options such as radiofrequency ablation (RFA) and focal laser ablation (FLA), among others, are considered to be in the early phases of evaluation [849].

High-intensity focused US consists of focused US waves emitted from a transducer that cause tissue damage by mechanical and thermal effects as well as by cavitation [851]. The goal of HIFU is to heat malignant tissue above 65°C, so that it is destroyed by coagulative necrosis. High-intensity focused US is performed under general or spinal anaesthesia, with the patient lying in the lateral or supine position. Since the ultrasound energy is most often delivered from the rectal cavity, HIFU faces challenges in delivering energy to the anterior part in large prostates.

Cryotherapy uses freezing techniques to induce cell death by dehydration resulting in protein denaturation, direct rupture of cellular membranes by ice crystals and vascular stasis and microthrombi, resulting in stagnation of the microcirculation with consecutive ischaemic apoptosis [846-848]. Freezing of the prostate is ensured by the placement of 17-gauge cryo-needles under TRUS guidance, placement of thermosensors at the level of the external sphincter and rectal wall and insertion of a urethral warmer. Two freeze-thaw cycles are used under TRUS guidance resulting in a temperature of -40°C in the mid-gland and at the neurovascular bundle. Currently, third and fourth generation cryotherapy devices are mainly used.

Irreversible electroporation (IRE) uses high-volage low-energy electric pulses applied among transperineally placed electrodes to induce nanopores within cell walls. These pores modify of cell membrane permeability and induce cell death by disruption of cellular homeostasis [852].

6.2.4.b Whole-gland therapies

Whole gland treatments using cryosurgery and HIFU were investigated as a replacement for surgery or radiotherapy, with limited success. The main adverse effects of whole-gland cryosurgery are ED (18%), urinary incontinence (2–20%), urethral sloughing (0–38%), rectal pain and bleeding (3%) and rectourethral fistula formation (0–6%) [853]. There is a lack of prospective comparative data regarding oncological outcomes of whole-gland cryosurgery as a curative treatment option for men with localised PCa, with most studies being non-comparative single-arm case series with short follow-up [853].

High-intensity focused US has previously been widely used for whole-gland therapy with the following adverse effects: acute urinary retention (10%), ED (23%), urethral stricture (8%), rectal pain or bleeding (11%), rectourethral fistula (0–5%) and urinary incontinence (10%) [853]. An SR including 375 retrospective and prospective trials with more than 6500 patients showed a wide variation of oncological and functional outcomes [854]. Combining whole-gland HIFU treatment with TURP has been shown to reduce the rate of urethral strictures and to maintain the level of incontinence, but to increase the rate of ED [855].

Overall, the lack of any long-term prospective comparative studies and data to suggest poor long-term oncological outcomes for men with high-risk localised disease [856] prevents whole-gland HIFU from being considered as a reasonable alternative to the established curative treatment options [853]. In addition, the expected improvements in functional outcome failed to materialise with 12% of patient developing incontinence and 61% developing ED [857].

6.2.4.c Focal therapy

Over the past two decades, there has been a trend towards earlier diagnosis of PCa as a result of greater public and professional awareness, leading to the adoption of both formal and informal screening strategies. The effect of this change has been that men are identified at an earlier stage with smaller tumours, with a greater propensity for unifocal disease [858-860]. There is also greater awareness of the risks of the consequences of treatment leading to attempts to ablate only a region of the prostate containing the tumour, thereby limiting toxicity by sparing the neurovascular bundles, sphincter, and urethra [861-863]. The question remains which if any of these small unifocal tumours require treatment.

An SR included data from 5,827 patients across 72 studies and covered various energy sources, including HIFU, cryotherapy, Photodynamic Therapy (PDT), laser interstitial thermotherapy, focal BT, irreversible electroporation (IRE) and radiofrequency ablation (RFA) [864]. The review favours HIFU and PDT for their higher quality data, over 95% of pad-free incontinence and 85–90% of patients without clinically significant cancer in short-term analysis. This must be critically analysed, because 45% of all patients with a focal approach included in this SR had an ISUP Grade GG 1 cancer. The overall quality of the evidence was low, due to most studies being single-

centre, non-comparative and retrospective in design, heterogeneity of definitions and approaches, follow-up strategies, outcomes and duration of follow-up. Although the review finds high-quality evidence that focal therapy has favourable functional outcomes and minimises AEs, definitive evidence of oncological benefit remains unavailable.

A more stringent SR including only prospective studies and per protocol posttreatment biopsies found that, after one year, 8.8% of patients had an infield failure with ≥ ISUP GG 2 cancers and 13.0% had ≥ ISUP GG 2 cancers anywhere in the prostate [865]. This work did not include any definition of clinically relevant cancer and included 35% of patients with ISUP GG 1 at initial diagnosis. Focal ablation showed only a 9% reduction in sexual function scores at one year, compared to 43% for whole-gland ablation.

At this time, the largest analysis on oncologic outcomes following focal HIFU includes 1,379 men with a median follow-up of 32 months (65% of patients were D'Amico intermediate risk and 28% high risk) [866]. In this study, one repeated focal HIFU session was allowed and performed in 18% of all patients. Parametric MRI was performed if consecutive PSA rises were identified and biopsies were offered if the mpMRI was suspicious. Eighty percent of patients had at least one follow-up mpMRI and 44% had a follow-up biopsy. The primary outcome was failure-free survival (FFS), which was defined as evidence of cancer requiring whole-gland salvage treatment. At seven years the FFS for intermediate- and high-risk cancers was 68% and 65%, respectively [866].

An SR on irreversible electroporation (IER) including 19 studies and 1,452 treated patients showed that the infield recurrence rate after one year was comparable to other focal therapy energy sources, with 0% - 39% in repeat biopsy [867]. Additionally, the clinically significant out-field cancer rate was high (0%-31%). The retreatment rate using IRE, radical prostatectomy, radiotherapy and HIFU was 8%-36%. While this review showed over 95% pad-fee patients after treatment. The assessment of erectile function by IIEF and EPIC showed greater heterogeneity and warrants a more detailed investigation. These findings were underlined by an international multicentre study with 411 patients confirming the good functional outcome with a four point drop in EEEF-5 at three months and residual ISUP GG 2 cancers found in 24.1% after one year. However, only a quarter of patients had a biopsy after IRE in this study [868].

There is currently no well-defined pathway for focal therapy or follow-up, and the field is still developing. The optimal energy source for tumours at various locations, the need for double treatments during initial therapy and the use of MRI or PSA for follow up are still a matter of research. The high rate of out-field recurrences after treatment indicates that the pretreatment evaluation should be maximised by targeted and systematic biopsies [865]. Whether modern imaging modalities (e.g. PSMA-PET) could support the mpMRI is not sufficiently evaluated. The Guideline panel acknowledges the challenges for interventional RCTs [869-871]. The interim analysis and meeting reports demonstrate slow recruitment, patients declining consent and rejecting their treatment allocation into the RP group (approx. 25%). In an attempt to overcome this challenge, propensity-matched analysis using prospective multicentre databases have been performed for comparison of focal therapy versus radical therapy [872, 873]. Such analyses are always susceptible to unmeasured selection biases in who was selected for each treatment.

Oncological follow-up data up to eight years can be used to counsel patients in treatment decisions [872, 873]. Patients managed by focal therapy had a HIFU or cryotherapy, with one retreatment, if required. Of these, 17.1% of patients in the focal arm received a retreatment. The primary outcome was FFS defined as 'need for local or systemic salvage treatment or metastasis'. Both groups included 246 patients with an average PSA of 7.9ng/mL and 60% ISUP GG 2/3 cancers. The cancer core length was 5–6mm, with 45% having bilateral cancer. The authors report similar cancer control eight years after therapy, with FFS and BCR of 83% and 23.9% for focal therapy versus 79% and 24.8% for RP, respectively. Comparable results were demonstrated in a cohort-based analysis with a follow-up of six years [873]. The use of various definitions for oncological failure in the two arms is another limitation of these studies. While any recurrence after RP was seen as failure, a second HIFU was permitted in the focal group. The current data from the HIFU Evaluation and Assessment of Treatment (HEAT) registry indicates that a repeat HIFU does not significantly decrease urinary or erectile function [874]. However, this change of failure definition will have to be re-evaluated. It is important to note, that these results were achieved in centres with a dedicated focal program in which all patients had an mpMRI with targeted and systematic biopsies or full template-mapping biopsies. Therefore, it seems necessary to perform systematic biopsies in patients who are candidates for focal therapy.

The impact of salvage therapies after focal therapy was investigated in small series in specialised centres [875, 876]. If a salvage RP is required after focal therapy, the reported functional and oncological outcomes are comparable to treatment-naive patients [877, 878]. In a recent SR including 482 patients from 12 studies, the authors conclude that, when compared to primary surgery, the salvage radical prostatectomy after focal therapy

has a higher PSM rate of 27% and a slightly worse incontinence rate. Although the early complication rate was also higher, most of them could be managed conservatively [879]. An SR of salvage radiotherapy after HIFU or cryotherapy was analysed showed a favourable toxicity profile and a comparable overall biochemical relapse rate of approximately 20% [880].

One comparative RCT was conducted in a very-low risk population for which there is currently a strong movement away from any form of active treatment. This study was comparing padeliporfin-based vascular targeted PDT versus AS and found at a median follow-up of 24 months that fewer patients progressed in the PDT arm compared with the AS arm (adjusted HR: 0.34, 95% CI: 0.24–0.46), and required less radical therapy (6% vs. 29%, p < 0.0001). Updated results were published in 2018, showing that these benefits were maintained after four years [881]. Nevertheless, limitations of the study include an unusually high observed rate of disease progression in the AS arm (58% in two years) and more patients in the AS arm chose to undergo radical therapy without a clinical indication, which may have introduced confounding bias. Finally, the AS arm did not undergo any confirmatory biopsy or any MRI scanning, which is not representative of contemporary practice. A matched-pair analysis comparing focal cryotherapy to AS with 76% ISUP GG 1 cancers failed to demonstrate any significant advantages for MFS and OS [882].

The available evidence indicates that focal therapy is associated with fewer AEs than whole-gland or radical treatments. Many of the patients included in these trials would currently be considered to have been overtreated. Robust prospective trials reporting standardised 15-year oncological outcomes [883] are needed in patients with clinically significant cancers before unrestricted recommendations in support of focal therapy for routine clinical practice can be made [849, 883, 884]. Currently, focal therapy using HIFU or cryotherapy should be performed within the context of a prospective registry.

All other ablative modalities and treatment strategies should only be offered in a well-designed prospective trial setting. To allow quality analysis of the collected data, the prospective registry should adhere to the EMA recommendations (Guideline on registry-based studies EMA/426390/2021), which emphasises the need for clear follow-up timelines and timely recording, completeness of core data of consecutive patients enrolled, an analysis plan in defined intervals and a data quality management.

6.3 Management by disease stages

6.3.1 Management of low-risk disease

6.3.1.a Watchful waiting

For patients with a life expectancy of < 10 years (based on comorbidities and age) for whom curative treatment would not be an option in the case of progression after AS, WW is standard of care.

6.3.1.b Active surveillance

Active surveillance should be considered standard of care for all patients with a life expectancy > 10 years (based on comorbidities and age) and where curative treatment would be considered in the case of disease progression.

6.3.1.b.1 Androgen deprivation monotherapy

The Early Prostate Cancer (EPC) Trial Programme found that, in patients with localised disease, ADT monotherapy did not improve PFS or OS in any of the subgroups compared with placebo [885]. Instead, there was a statistically insignificant numerical trend towards worse OS with ADT in the WW subgroup (HR: 1.16, 95% CI: 0.99–1.37; p = 0.07). Although the trial did not directly address men with low-risk disease, it offered some evidence suggesting that otherwise asymptomatic men with localised disease should not receive ADT monotherapy.

6.3.1.c Other therapeutic options

Other treatments, such as whole-gland therapy (e.g. RP or RT) or focal ablative therapy, remain highly likely to be overtreatment in the setting of low-risk disease and should not be used outside a trial setting.

6.3.1.d Recommendations for the management of low-risk disease

Recommendations	Strength rating
Manage patients with a life expectancy < 10 years with watchful waiting.	Strong
Manage patients with a life expectancy > 10 years and low-risk disease with active surveillance.	Strong

6.3.2 *Management of intermediate-risk disease*

6.3.2.a Watchful waiting

For patients with a life expectancy of < 10 years (based on comorbidities and age), where curative treatment is not a direct option or would not be an option in the case of progression after AS, WW is standard of care.

6.3.2.b Active Surveillance

Although men with less-favourable disease characteristics have worse outcomes after any treatment, the question is whether a delay in curative treatment due to initial active surveillance leads to additionally unfavourable outcomes. Intuitively, the higher risk disease, the higher risk of adverse outcomes due to an initial delay. Inclusion is based on favourable disease characteristics as discussed in Section 6.2.1.b.2.

6.3.2.c Radical prostatectomy

Patients with intermediate-risk PCa should be informed about the results of two RCTs (SPCG-4 and PIVOT) comparing RP versus WW in localised PCa. In the SPCG-4 study, death from any cause (RR: 0.71, 95% CI: 0.53–0.95), death from PCa (RR: 0.38, 95% CI: 0.23–0.62) and distant metastases (RR: 0.49, 95% CI: 0.32–0.74) were significantly reduced in intermediate-risk PCa at 18 years. After 30-years follow-up overall (not risk-stratified), RP reduced death from any cause (RR: 0.74, 95% CI: 0.64–0.87), and death from PCa (RR: 0.52, 95% CI: 0.40–0.67) for a mean of 2.2 life years (95%CI 1.4-2.9) gained [886]. Survival benefit was most likely if alive for more than 20 years, with a number needed to treat to avert one PCa death of six [887]. In the PIVOT trial, according to a preplanned subgroup analysis among men with intermediate-risk tumours, RP significantly reduced all-cause mortality (HR: 0.69, 95% CI: 0.49–0.98), but not death from PCa (0.50, 95% CI: 0.21–1.21) at ten years [888]. In the ProtecT trial, 24% of the population were intermediate risk (at baseline) and no significant difference in prostate cancer deaths was seen for RP versus active monitoring (with delayed active treatment, HR 0.68 (0.11–4.05). A meta-analysis based on the findings of SPCG-4, PIVOT and ProtecT demonstrated a benefit from RP over-observation with a significantly decreased risk of death of 9% and of disease progression of 43% [889]. However, no stratification by disease stages was performed. A large study found 2.9% of LN invasion in a contemporary cohort of 6,883 patients undergoing RP and LND for intermediate risk PCa [890].

6.3.2.d Radiation therapy

6.3.2.d.1 IMRT/VMAT

Ultra-hypofractionated IMRT/IGRT or SBRT, using either 36.25Gy (40Gy to prostate) in 5fx or 42.7Gy in 7fx, can be offered to patients with NCCN-favourable intermediate and good urinary function. Additional ADT is not required in GG2 disease [786]. Patients undergoing conventional or moderate hypofractionation and suitable for ADT can be treated with short-term ADT (four to six months) [891-893]. The RTOG 0815 RCT demonstrated improved BRFS, metastasis-free and prostate CSS with the addition of six-months ADT to dose-escalated RT [802]. For patients unsuitable (e.g. due to comorbidities) or unwilling to accept ADT (e.g. to preserve their sexual health), the recommended treatment is IMRT/VMAT (76–78Gy or equivalent moderate HFX) or a combination of IMRT/VMAT and BT, as described below. A secondary analysis of the PCS III trial has suggested that patients with NCCN-favourable intermediate-risk disease can safely omit ADT if their RT dose is 76Gy, but this is based on an unplanned subgroup analysis and only 138 patients had favourable intermediate-risk disease [801]. An individual discussion between the physician and the patient of the possible benefits and harms of omitting ADT in this group is essential [778].

6.3.2.d.2 Brachytherapy

Systematic review recommends LDR BT monotherapy can be offered to patients with NCCN-favourable intermediate-risk disease and good urinary function (see Section 4.4) [894]. Fractionated HDR BT as monotherapy can be offered to selected patients with intermediate-risk PCa, although they should be informed that results are only available from small series in very experienced centres. Five-year PSA control rates over 90% are reported, with late grade 3+ GU toxicity rates < 5% and no, or very minimal, grade 3+ GI toxicity rates [841]. There are no direct data to inform on the use of ADT in this setting. Trimodality therapy with IMRT plus BT boost and short-term ADT can be considered for NCCN-unfavourable intermediate-risk PCa (see Section 6.2.3.d), but patients should be made aware that the potential improvements in biochemical control are accompanied with an increased risk of long-term urinary problems [830, 832, 837].

6.3.2.e Other therapeutic options

6.3.2.e.1 Focal therapy

The available evidence indicates that focal therapy is associated with less AEs than whole gland or radical treatments. Robust prospective trials reporting standardised fifteen-year oncological outcomes [883], are needed in patients with clinically significant cancers before unrestricted recommendations in support of focal therapy for routine clinical practice can be made [849, 883, 884].

6.3.2.e.2 *Androgen deprivation therapy monotherapy*

Data regarding the use of ADT monotherapy for intermediate-risk disease have been inferred indirectly from the EORTC 30891 trial, which was an RCT comparing deferred ADT versus immediate ADT in 985 patients with T0–4 N0–2 M0 disease [895]. The trial showed a small, but statistically significant, difference in OS in favour of immediate ADT monotherapy, but there was no significant difference in CSS, predominantly because the risk of cancer-specific mortality was low in patients with PSA < 8ng/mL. Consequently, the use of ADT monotherapy for this group of patients is not considered standard, even if they are not eligible for radical treatment.

6.3.2.f Recommendations for the management of intermediate-risk disease*

Recommendations	Strength rating
Expectant management	
Offer watchful waiting in asymptomatic patients with life expectancy < 10 years (based on co-morbidities and age).	Strong
Offer active surveillance (AS) to selected patients with ISUP grade group (GG) 2 disease, e.g. < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low extent of tumour in biopsies (≤ 3 positive cores with ISUP GG 2 and ≤ 50% cancer involvement/core) or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
Patients with ISUP GG 3 disease should be excluded from AS protocols.	Strong
Reclassify patients with low-volume ISUP GG 2 disease included in AS protocols if repeat non-magnetic resonance imaging (MRI)-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum cancer involvement > 50%/core of ISUP GG 2 disease.	Weak
Radical prostatectomy (RP)	
Offer RP to patients with a life expectancy of > ten years.	Strong
Offer nerve-sparing surgery to patients with a low risk of extracapsular disease on that side.	Strong
Radiotherapeutic treatment	
Offer low-dose rate (LDR) brachytherapy to patients with good urinary function and NCCN-favourable intermediate-risk disease.	Strong
Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in four weeks or 70 Gy/28 fx in six weeks), in combination with short-term androgen deprivation therapy (ADT) (four to six months).	Strong
Offer focal boosting to MRI-defined dominant intraprostatic tumour when using conventionally fractionated IMRT/IGRT (1.8-2.0 Gy per fraction), ensuring that Organ at Risk constraints are not exceeded.	Weak
Offer ultra-hypofractionated IMRT/IGRT or stereotactic body radiation therapy, using either 36.25 Gy (40 Gy to prostate) in 5 fx or 42.7 Gy in 7 fx delivered alternate days in patients with favourable intermediate risk considering urinary function.	Weak
Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk disease, in combination with short-term ADT (four to six months).	Weak
Offer high-dose rate brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk disease in combination with short-term ADT (four to six months).	Weak
Other therapeutic options	
Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal ablative therapy within clinical trials or registries.	Strong
Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Weak

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

6.3.3 *Management of high-risk localised disease*

Patients with high-risk PCa are at an increased risk of PSA failure, need for secondary therapy, metastatic progression and death from PCa. Nevertheless, not all high-risk PCa patients have a uniformly poor prognosis after RP [896]. When managed with noncurative intent, high-risk PCa is associated with 10-year and 15-year PCSM rates of 28.8 and 35.5%, respectively [897]. There is no consensus regarding the optimal treatment of men with high-risk PCa.

Some evidence suggests that radical treatment for high-risk PCa can be delayed up to three months after the diagnosis without any oncological consequences [898, 899]. Systematic reviews suggest that there is a higher risk of biochemical recurrence and worse pathological outcomes when definitive treatment is given beyond a six- to nine-months delay. However, there is no conclusive data regarding stronger endpoints (CSS or OS).

6.3.3.a Radical prostatectomy

Radical prostatectomy is a standard option in selected patients with a low tumour volume, provided that the tumour is not fixed to the pelvic wall or there is no invasion of the urethral sphincter. Patients should be aware preoperatively that surgery may be part of multimodal treatment, with adjuvant SRT or ADT; however, almost half of patients will be free from recurrence without multimodal treatment at five years [900, 901]. Neoadjuvant therapy using ADT is not indicated [902].

6.3.3.b External beam radiation therapy

For high-risk localised PCa, a combined modality approach should be used consisting of IMRT/VMAT plus long-term ADT. The duration of ADT must take into account PS, comorbidities and the number of poor prognostic factors. It is important to recognise that in several studies, EBRT plus short-term ADT did not improve OS in high-risk localised PCa and long-term ADT (at least two to three years) is currently recommended for these patients [794, 795, 803]. Moderate HFX is an option in high-risk patients with localised disease. The CHHiP study included 12% high-risk patients (n = 386), but limited entry to those with a PSA < 30ng/mL and a Roach formula risk of SV involvement < 30% [774]. Patients were ineligible if they had both T3a tumours and ISUP grade group 4 or higher. The PCS-5 RCT used moderate HFX and elective nodal irradiation and efficacy was equivalent in both groups [781, 782].

6.3.3.b.1 Lymph node irradiation in cN0

There is no clear evidence for prophylactic irradiation of the pelvic LNs in intermediate- and high-risk disease. The long-term results of the NRG/RTOG 9413-trial, which randomised intermediate-risk and high-risk localised PCa patients (1,322 cN0 patients were enrolled), showed that neoadjuvant HT plus whole pelvic RT improved PFS only compared with neoadjuvant ADT plus prostate RT and whole pelvic RT plus adjuvant ADT [903]. However, at the increased risk of ≥ grade 3 GI-toxicity.

A well-conducted single-centre RCT randomised 224 patients comparing prostate-only RT (PORT) versus whole pelvic RT (WPRT) in localised high-risk- and locally advanced tumours (cN0) with a risk of > 20% of positive nodes (Roach formula). With a median follow-up of 68 months, there was a significant improvement of distant MFS (95.9% vs. 89.2%, HR: 0.35, p = 0.01) and DFS (89.5% vs.77.2%, p = 0.02). However, there was a significant higher rate of late GU ≥ 2 effects (17.7% vs. 7.5%, p = 0.02), the trial was relatively small in size with additional limitations and these findings are therefore insufficient to define a change in practice [904, 905]. The benefits of pelvic nodal irradiation using IMRT/VMAT merit further investigation in large scale RCTs.

6.3.3.b.2 Brachytherapy boost

In men with NCCN-unfavourable intermediate- or high-risk PCa, BT boost with supplemental EBRT and HT may be considered. See Sections 6.2.3.d.1 and 6.2.3.d.2 for details on RCTs comparing EBRT alone and EBRT with LDR or HDR boost, respectively.

6.3.3.c Recommendations for the management of high-risk localised disease*

Recommendations	Strength rating
Expectant management	
Offer watchful waiting to asymptomatic patients with life expectancy < 10 years.	Strong
Radical prostatectomy (RP)	
Offer RP to selected patients.	Strong

Extended pelvic lymph node dissection (ePLND)	
In patients undergoing a lymph node dissection you should perform an ePLND.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure.	Strong
Radiotherapeutic treatment	
Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in four weeks or 70 Gy/28 fx in six weeks), in combination with long-term androgen deprivation therapy (ADT) (two to three years).	Strong
Offer focal boosting to magnetic resonance imaging (MRI)-defined dominant intraprostatic tumour when using normo-fractionated IMRT/IGRT (1.8-2.0 Gy per fraction) ensuring that Organ at Risk constraints are not exceeded.	Strong
Offer patients with good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate) in combination with long-term ADT (two to three years).	Weak
Other therapeutic options	
Do not offer either whole gland or focal therapy.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly differentiated tumour.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

6.3.4 Management of locally advanced PCa

In the absence of high-level evidence, an SR could not define the most optimal treatment option [906]. Randomised controlled trials are only available for EBRT. A local treatment combined with a systemic treatment provides the best outcome, provided the patient is fit enough to receive both. The initial results of the SCPG-15 trials suggested that randomisation between surgery and EBRT is feasible, but oncologic outcomes are awaited [907].

6.3.4.a Radical prostatectomy

Surgery for locally advanced disease as part of a multimodal therapy has been reported [897, 908, 909]. However, the comparative oncological effectiveness of RP as part of a multimodal treatment strategy versus upfront EBRT with ADT for locally advanced PCa remains unknown. A prospective phase III RCT (SPCG-15) comparing RP (with or without adjuvant or salvage EBRT) against primary EBRT and ADT among patients with locally advanced (T3) disease is currently recruiting [910]. Data from retrospective case series demonstrated over 60% CSS at 15 years and over 75% OS at ten years [877, 897, 900, 908, 909, 911, 912]. For cT3b–T4 disease, PCa cohort studies showed 10-year CSS of over 87% and OS of 65% [878, 913]. The indication for RP in all previously described stages assumes the absence of clinically detectable nodal involvement (cN0), based on conventional imaging. In case of suspected positive LNs during RP (initially considered cN0) the procedure should not be abandoned, since RP may have a survival benefit in these patients. Intraoperative frozen section analysis is not justified in this case [534].

6.3.4.b Treatment of cN1 M0 PCa

Lymph-node-metastasised PCa is an entity in which options for local therapy and systemic therapies overlap. Approximately 5 to 10% of newly diagnosed PCa patients have synchronous suspected pelvic nodal metastases on conventional imaging (CT/bone scan) without bone or visceral metastases (cN1 M0 stage). Individual patient data from RCTs of RT plus long term ADT indicate that cN1 disease carries highest risk of metastasis (HR 1.86 [1.56–2.21]; five-year MFS 67%, ten-year MFS 36%) and death (HR 1.77 [1.45–2.15], ten-year OS 47%) among patients with high-risk localised/locoregional disease [914].

6.3.4.b.1 Consideration of molecular imaging

Meta-analyses have shown that molecular imaging, such as PSMA-PET/CT, prior to primary treatment in advanced PCa detected disease outside the prostate in 32% of cases despite prior negative conventional imaging using bone scan and pelvic CT/MRI [514]. A RCT assessing PSMA-PET/CT as staging tool in high-risk PCa confirmed these findings and showed a 32% increase in accuracy compared with conventional imaging for the detection of pelvic nodal metastases [553]. Notably, more sensitive imaging also caused a stage shift with more cases classified as N1 on “molecular imaging” (miN1), but with, on average, lower nodal disease burden

compared to cases classified as cN1. After follow-up (median 41 months), miN1 status was prognostic for treatment failure (adjusted HR 2.0 [1.10–3.64], p = 0.007), but N1 status per conventional imaging was not (HR 0.6 [0.1–2.4], p = 0.45) [915].

The definition of miN1 is a subject of ongoing discussion, given that multiple guidelines exist because detection can be influenced by size of the lymph nodes and PSMA expression [114, 916, 917]. For patients with high or equivocal PSMA expression but normal size (< 10 mm), there is a lack of knowledge of the best treatment option and prospective data are encouraged [918].

6.3.4.b.2 Local treatment of cN1 M0 PCa

The management of cN1M0 PCa is historically based on long-term ADT combined with a local treatment with radiotherapy more commonly used than RP/pelvic nodal dissection. No randomised evidence is available and the potential benefit of adding local treatment to ADT has been assessed in a nonrandomised post-hoc analysis of STAMPEDE and retrospective studies summarised by Yaow *et al.* [919]. Pooled meta-analysis was performed for local treatment versus no local treatment (four studies, n = 4,597, local treatment n = 2,646) and showed improved estimated overall survival at all time points to 10 years (OR: 1.49-1.81). The majority of patients underwent RT as local therapy. Assessment of RT versus no local therapy (four studies, n=3,768) showed similar estimates for improvements in overall survival. Not included in this pooled analysis was STAMPEDE control arm data, which showed improvements in failure-free survival (adjusted HR: 0.48, 95% CI: 0.29-0.79) without severe toxicity [920] at median follow-up of 17 months. Comparisons between local treatment modalities were limited by inclusion of retrospective studies, which fail to describe clearly how cN1 was defined.

Local treatment of cN1M0 disease in the era of taxane chemotherapy and ARPIs is understudied. Extended follow-up of STAMPEDE, reported as exploratory sub-analyses of patients who received docetaxel or control according to receipt of RT after median follow-up of 81.2 months, maintained failure-free survival benefit (HR: 0.68) in N+ patients but no prostate cancer-specific survival (HR: 0.81) or overall survival (HR: 0.77) benefit was demonstrated [921]. Greatest benefits from RT were seen in the control (without docetaxel) group, because no significant benefits of RT receipt were seen in any category for the docetaxel group. Two RCTs from the STAMPEDE platform protocol reported a pre-planned meta-analysis of men with *de novo* high-risk/locally advanced M0 disease or relapse after primary curative therapy with high-risk features. Thirty-nine percent of patients (n = 774) were N1 on conventional imaging [922]. Radiotherapy in addition to long-term ADT was administered in at least 71% of N1 patients. Data on survival according to whether RT was planned in N1 patients was not presented.

6.3.4.b.3 Systemic treatment of cN1 M0 PCa

The intensification of systemic treatment from initial ADT to other agents has been assessed within data from the STAMPEDE multi-arm RCT with a preplanned meta-analysis in M0 patients. In cN1 M0 patients (39% of the cohort), improved metastasis-free (HR: 0.49, 95% CI: 0.38-0.64) and overall (HR: 0.53, 95% CI: 0.39-0.70) survival was observed with intensification (abiraterone and enzalutamide or abiraterone alone) above standard of care (ADT +/- prostate radiotherapy in 85% of the whole cohort) in cN1M0 patients [922].

Considering intensification with docetaxel, exploratory sub-analyses of STAMPEDE nonmetastatic (cN0/N1M0) patients who received docetaxel or control showed failure-free survival benefit (HR: 0.70, 95% CI: 0.56-0.88), but no metastatic progression-free (HR: 0.89) or overall survival (HR: 0.88) benefit [921]. Similar trends were observed in the N0 and N+ subgroups. Radiotherapy was delivered to 77% of the cohort (see Section 6.3.4.b). The AFU-GETUG 12 trial compared the impact of docetaxel plus estramustine in addition to ADT and 29% of included high-risk non-metastatic PCa patients had a nodal involvement (pN1) at randomisation [923]. Relapse-free survival rates were higher for cN1 patients receiving docetaxel plus estramustine but did not achieve statistical significance (HR: 0.66; 86 0.43–1.01). A meta-analysis of docetaxel trials in N0/N1-M0 patients showed an 8% four-year failure-free survival advantage for docetaxel compared with ADT alone without OS benefit (HR: 0.87, 95% CI: 0.69-1.09) [924].

Given the MFS and OS benefits observed in the overall population (see Section 6.3.4.b), additional abiraterone (for 2 years) above standard of care (combined ADT for 3 years with prostate +/- WPRT) should be a SOC in cN1 patients.

Table 6.3.1: Selected studies assessing local treatment in (any cT) cN1 M0 prostate cancer patients

Study	n	Design	Study period/ follow-up	Treatment arms	Effect on survival
ADT only					
Bryant, *et al.* 2018 [925]	648	Retrospective (National Veterans Affairs)	2000-2015 61 mo.	ADT ± EBRT	Significant benefit for combined treatment only if PSA levels less than the median (26ng/mL) All-cause mortality HR: 0.50 CSS, HR: 0.38
Sarkar, *et al.* 2019 [926]	741	Retrospective (National Veterans Affairs)	2000-2015 51 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for RP All-cause mortality HR 0.36 CSS, HR: 0.32 No statistical difference for RP vs. RT ($p \geq 0.1$) All-cause mortality HR: 047 CSS, HR: 0.88
Lin, *et al.* 2015 [927]	983 before propensity score matching	Retrospective (NCDB)	2004-2006 48 mo.	ADT ± EBRT	Significant benefit for combined treatment 5-yr. OS: 73% vs. 52% HR: 0.5
Tward, *et al.* 2013 [928]	1,100	Retrospective (SEER)	1988-2006 64 mo.	EBRT (n = 397) vs. no EBRT (n=703) No information on ADT)	Significant benefit for EBRT 5-yr. CSS: 78% vs. 71% HR: 0.66 5-yr. OS: 68% vs. 56%, HR: 0.70
Rusthoven, *et al.* 2014 [929]	796	Retrospective (SEER)	1995-2005 61 mo.	EBRT vs. no EBRT (no information on ADT)	Significant benefit for EBRT 10-yr. OS: 45% vs. 29% HR: 0.58
Seisen, *et al.* 2018 [930]	1,987	Retrospective (NCDB)	2003-2011 50 mo.	ADT ± local treatment (surgery or RT)	Significant benefit for combined treatment 5-yr. OS: 78.8% vs. 49.2% HR: 0.31 No difference between RP and RT
Chierigo, *et al.* 2022 [931]	4,685	Retrospective (SEER)	2004-2016	RP or RT (unknown ADT status)	Propensity score matching 5-yr OS: 84.6% (RP) vs. 75% (RT), HR 0.62, $p < 0.001$ 5-yr CSS: 90.7% (RP) vs. 83% (RT), HR 0.62, $p < 0.001$ 5-yr other cause mortality, 6.1% RP vs. 8.0% RT, HR 0.71, $p = 0.04$
James, *et al.* 2016 [920]	177	Unplanned subgroup analysis RCT	2005-2014 17 mo.	ADT ± EBRT (EBRT encouraged)	Significant benefit for combined treatment 5-yr. OS: 93% vs. 71% 2-yr. FFS: 81% vs. 53% FFS, HR: 0.48

Elumalai, *et al.* 2023 [932]	337	Retrospective 4 centres UK	2022-2019	ADT +/- EBRT	Significant benefit for combined treatment 5-yr.OS: 87% vs. 56% HR: 0.27 5-yr. BPFS: 74.1% vs. 34.2% HR: 0.33
Other systemic therapies					
James, *et al.* 2022 [921]	258 (N1 patients)	Planned subgroup analysis RCT	2005-2018 81.2 mo	Standard of care (ADT +/- EBRT) +/- docetaxel (EBRT planned for 55% SOC, 40% of docetaxel)	5-year estimated Metastatic PFS (SOC + docetaxel vs SOC, HR: 0.79) OS (RT 78% vs. no RT 71%, HR: 0.77)* CSS (RT 84% vs. no RT 79%, HR: 0.81)* FFS (RT 51% vs. no RT 36%, HR: 0.68)* *No stratification for docetaxel use
Attard, *et al.* 2022 [922]	774 (N1)	Planned subgroup analysis RCT	2011-2016 72 mo	Standard of care (ADT +/- EBRT) +/- Abiraterone with or without enzalutamide (EBRT planned for 71% of N1 patients)	MFS (SOC + Abiraterone with or without enzalutamide vs SOC alone, HR: 0.49, 95% CI: 0.38-0.64) OS (SOC + Abiraterone with or without enzalutamide vs SOC alone, HR: 0.53, 95% CI: 0.39-0.70)

ADT = androgen deprivation therapy; BPFS = biochemical progression-free survival; CSS = cancer-specific survival; EBRT = external beam radiotherapy; FFS = failure-free survival; HR = hazard ratio; mo. = months; n = number of patients; OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; yr. = years.

6.3.4.c Options other than surgery or radiotherapy for primary treatment

6.3.4.c.1 Investigational therapies

Cryotherapy, HIFU and focal therapies currently have no place in the management of locally advanced PCa.

6.3.4.c.2 Androgen deprivation therapy monotherapy

The deferred use of ADT as single treatment modality was answered by the EORTC 30891 trial [895]. Nine hundred and eighty-five patients with T0–4 N0–2 M0 PCa received ADT alone, either immediately or after symptomatic progression or occurrence of serious complications. After a median follow-up of 12.8 years, the OS favoured immediate treatment (HR: 1.21, 95% CI: 1.05–1.39). Surprisingly, no different disease-free or symptom-free survival was observed, raising the question of survival benefit. In locally advanced T3–T4 M0 HSPC unsuitable for surgery or RT, immediate ADT may only benefit patients with a PSA > 50ng/mL and a PSA-DT < twelve months or those that are symptomatic [895, 933]. The median time to start deferred treatment was seven years. In the deferred treatment arm, 25.6% of patients died without needing treatment.

Patients with locally-advanced disease are more likely to require multi-modality therapy which might delivered sequentially (e.g. RP followed by ADT with or without RT) or in combination (e.g. RT plus ADT plus abiraterone). There is currently no randomised data to inform patients or clinicians which of these strategies is the most effective and an open discussion about the risks and benefits is important to allow shared-decision making.

6.3.4.d Recommendations for management of locally advanced disease*

Recommendations	Strength rating
Radical prostatectomy (RP)	
Offer RP to selected patients with cN0 disease as part of multi-modal therapy.	Weak
Extended pelvic lymph node dissection (ePLND)	
In patients undergoing a lymph node dissection you should perform an ePLND.	Strong

Radiotherapeutic treatments	
Offer patients with cN0 disease intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy in combination with long-term androgen deprivation therapy (ADT).	Strong
Offer patients with cN0 disease and good urinary function, IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT.	Weak
Offer long-term ADT for at least two years.	Strong
Offer IMRT/VMAT plus IGRT to the prostate in combination with long-term ADT and two years of abiraterone to cN0M0 patients with ≥ 2 high-risk factors (cT3-4, Gleason ≥ 8 or prostate-specific antigen ≥ 40 ng/mL).	Strong
Offer IMRT/VMAT plus IGRT to the prostate plus pelvis in combination with long-term ADT and two years of abiraterone to cN1M0 patients.	Strong
Other therapeutic options	
Do not offer whole gland treatment or focal treatment.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

6.3.5 Adjuvant treatment after radical prostatectomy

6.3.5.a Introduction

Adjuvant treatment is, by definition, additional to the primary or initial therapy with the aim of decreasing the risk of relapse, despite the apparent full control following surgery. A postoperative detectable PSA is an indication of persistent prostate cells (see Section 6.3.6). All information listed below refers to patients with a postoperative undetectable PSA.

6.3.5.b Risk factors for relapse

Patients with ISUP GG > 2 in combination with EPE (pT3a), and particularly those with SV invasion (pT3b) and/or positive surgical margins, are at high risk of progression, which can be as high as 50% after five years [934]. Irrespective of the pT stage, the number of removed nodes [935-942], tumour volume within the LNs and capsular perforation of the nodal metastases are predictors of early recurrence after RP for pN1 disease [943]. An LN density (defined as 'the percentage of positive LNs in relation to the total number of analysed/removed LNs') of over 20% was found to be associated with poor prognosis [944]. The number of involved nodes appears to be a major factor for predicting relapse [937, 938, 945]; the threshold considered is less than three positive nodes from an ePLND [521, 937, 945]. However, prospective data are needed before defining a definitive threshold value.

6.3.5.b.1 Biomarker-based risk stratification after radical prostatectomy

The Decipher® gene signature consists of a 22-gene panel representing multiple biological pathways and was developed to predict systemic progression after definitive treatment. A meta-analysis of five studies analysed the performance of the Decipher® Genomic Classifier (GC) test on men post-RP. The authors showed in multivariable analysis that Decipher® GC remained a statistically significant predictor of metastasis (HR: 1.30, 95% CI: 1.14–1.47, p < 0.001) per 0.1 unit increase in score and concluded that it can independently improve prognostication of patients post-RP within nearly all clinicopathologic, demographic and treatment subgroups [946]. An SR of the evidence for the Decipher® GC has confirmed the clinical utility of this test in post-RP decision-making [947]. Further studies are needed to establish how to best incorporate Decipher® GC in clinical decision-making.

6.3.5.c Immediate (adjuvant) postoperative external irradiation after RP (cN0 or pN0)

Four prospective RCTs have assessed the role of immediate postoperative RT (adjuvant RT [ART]) (undetectable PSA mostly defined as PSA < 0.1ng/mL), demonstrating an advantage (endpoint, development of BCR) in high-risk patients (e.g. pT2 with positive surgical margins and ISUP grade group 3–5 or pT3/4 with or without positive surgical margins and ISUP grade group 3–5) post-RP (Table 6.3.2). In the ARO 96-02 trial, 80% of the pT3/R1/GS 8–10 patients randomised to observation developed BCR within ten years [948]. It must be emphasised that PSA was undetectable at inclusion only in the ARO 96-02 trial, which presents a major limitation interpreting these findings as patients with a detectable PSA would now be considered for salvage therapy rather than ART [948].

6.3.5.d Comparison of adjuvant and salvage radiotherapy

Two retrospective matched studies (510 and 149 patients receiving ART) failed to show an advantage for MFS [949, 950]. However, both studies were underpowered for high-risk patients (pT3b/R1/ISUP grade group 4–5 PCa). In contrast to these studies, a propensity score-matched retrospective analysis of two cohorts of 366 pT3 and/or R1 patients found that compared to SRT at a PSA between 0.1 and 0.5ng/mL, ART given at an undetectable PSA (< 0.1ng/mL) improved all three endpoints: BCR, MFS and OS [951].

Both approaches (ART and early SRT), together with the efficacy of adjuvant ADT, are compared in three prospective RCTs: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) trial [952]; the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES) trial [953]; and the Groupe d'Etude des Tumeurs Uro- Genitales (GETUG-AFU 17) trial [954]. In addition, a preplanned meta-analysis of all three trials has been published (Table 6.3.3) [955].

Two trials closed early after randomising 333/470 patients (RAVES) and 424/718 (GETUG-AFU-17) patients. RADICALS-RT included 1,396 patients, 93% (648/697) in the ART group. At the time of the ten-year analysis, 39% (270/699) of the Savage-RT-Policy Group started SRT with a median pre-SRT PSA-level of 0.2ng/ml. With the option of subsequent inclusion in RADICALS-HT, 154/649 (24%) of patients starting in the adjuvant RT group also received neoadjuvant or adjuvant HT: 90 patients for six months, 45 patients for two years and 19 patients outside RADICALS-HT. From the SRT group, 61/228 (27%) received neoadjuvant or adjuvant HT for six months (n = 33) and two years (n = 13). Fifteen of these patients were treated outside the trial [952]. All men in the GETUG-AFU-17 trial (n = 424) received six months of HT. Altogether, 684 out of 2,153 patients received additional ADT for at least six months across both trials [955]. Radiotherapy to the pelvic lymphatics was permitted in the GETUG-AFU and in the RADICALS-RT trials.

The primary endpoint for RAVES and GETUG-AFU 17 was biochemical PFS, while the primary endpoint for RADICALS-RT was MFS. So far, only RADICALS-RT have reported the ten-year primary endpoint data [956]. With a median follow up of 7.8 years, the 10-year FFDM was 93% (ART) versus 90% (SRT) (HR 0.68, p = 0.095), although based upon just 80 events in 1,396 patients. BPFS and OS also showed no significant difference (Table 6.3.3). With a median follow-up of between 4.9 years and 6.25 years in the ARTISTIC-Meta-analysis, no statistically significant difference was found for biochemical PFS for both treatments in all three trials (see Table 6.2.3). Additionally, there was a significant lower rate of grade ≥ 2 GU late side effects and grade 3–4 urethral strictures in favour of early SRT, which may also be caused by the low number of patients with PSA-progression and subsequent need for early SRT at the time of analysis (40% of patients) [955]. It should be noted that the side-effect profile may have been impacted with a larger proportion of ART patients receiving treatment with older 3D-treatment planning techniques as compared to SRT patients (GETUG-AFU 17: ART, 69% 3D vs. 46% SRT), and patients treated more recently were more likely to undergo IMRT techniques with a proven lower rate of late side effects [746]. Based on these three trials, however, patients with 'low risk factors' of biochemical progression after RP should be closely followed up with ultrasensitive assays and SRT should be discussed, if needed, as soon as PSA starts to rise, which must be confirmed by a second PSA measurement.

The proportion of patients with adverse pathology at RP (ISUP GG 4–5 and pT3 with or without positive margins) in all three trials was low (between 10–20%), and therefore even the meta-analysis may be underpowered to show an outcome in favour of SRT [955, 957, 958]. The subset analysis of this primary endpoint based on the pre-randomisation strata (i.e. the high-risk features ISUP GG 4 vs. ISUP GG 1-3 and pT3b-4 vs. ≤ pT3a) is still awaited to indicate whether these high-risk groups benefit from ART compared with SRT. However, a retrospective multi-centre study comparing ART and SRT in 26,118 patients, 2,424 of whom had high-risk features (pN1 or ISUP GG 4–5 and pT3/4 tumours) after RP [959], does support ART. With a median follow-up of 8.2 years and after excluding men with persistent PSA after RP ART showed a significantly lower acute mortality risk when compared with early SRT (p = 0.02, HR: 0.33). Therefore, ART continues to be a recommended treatment option in highly selected patients with adverse pathology ('high-risk patients'), i.e. ISUP GG 4–5 and pT3 with or without positive margins [960, 961].

In conclusion, the vast majority of patients with an undetectable PSA (< 0.1ng/ml) after RP do not need ART. However, in patients with high risk factors (pT3/4 and ISUP GG 4-5), ART to the prostatic bed should be given as they were under-represented in RADICALS, as well as in the meta-analysis [952-955] on the one hand, and the proven effect in RCT's on the other [948, 962, 963].

Table 6.3.2: Overview of all four randomised trials for adjuvant surgical bed radiation therapy after RP* (without ADT)

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (mo.)	Biochemical Progression-free survival	Overall survival
SWOG 8794 2009 [962]	431	pT3 cN0 ± involved SM	60-64Gy vs. observation	> 0.4	152	10 yr.: 53% vs. 30% (p < 0.05)	10 yr.: 74% vs. 66% Median time: 15.2 vs. 13.3 yr., p = 0.023
EORTC 22911 2012 [963]	1,005	pT3 ± involved SM pN0 pT2 involved SM pN0	60Gy vs. observation	> 0.2	127	10 yr.: 60.6% vs. 41% (p < 0.001)	81% vs. 77% n.s.
ARO 96-02 2014 [948]	388	pT3 (± involved SM) pN0 PSA post-RP undetectable	60Gy vs. observation	> 0.05 + confirmation	112	10 yr.: 56% vs. 35% (p = 0.0001)	10 yr.: 82% vs. 86% n.s.
FinnProstate Group 2019 [964]	250	pT2,R1/ pT3a	66.6Gy vs. observation (+ SRT)	> 0.4 (in 2 successive measure-ments)	112 vs. 103 (patients alive)	10 yr.: 82% vs. 61% p < 0.001	10 yr.: 92% vs. 87% n.s.

**See Section 6.3.5 for delayed (salvage) post-radical prostatectomy external irradiation.*
BCR = biochemical recurrence; FU = follow-up; mo. = months; n = number of patients; n.s. = not significant; PSA = prostate-specific antigen; RP = radical prostatectomy; SM = surgical margin; SRT = salvage radiotherapy.

Table 6.3.3: Overview of all three randomised trials and one meta-analysis for patients treated with adjuvant vs. early salvage RT after RP

Study	n	Inclusion criteria	Randomisation	Definition of BCR PSA (ng/mL)	Median FU (yr)	BPFS	OS or MFS	Side effects
RAVES TROG 08.03/ ANZUP 2020 [953]	333 target was 470 closed early	pT3a/ pT3b any T - SM+PSA post-RP: < 0.1ng/mL	64Gy ART PSA: < 0.1ng/mL vs. 64Gy early SRT at PSA > 0.2ng/mL med. pre-SRT: n.r.	> 0.4 post RT	6.1	5 yr.: 86% vs. 87% (p > 0.05)	n.r.	LT grade ≥ GU: 70% vs. 54% (p = 0.002)
RADICALS-RT [952]	1,396	pT3a/pT3b/ pT4 or PSA > 10ng/mL or pre-RP or any T, SM+ or Gleason 7-10. PSA post RP: < 0.2ng/mL	52.5Gy (20Fx) or 66Gy (33Fx) ART early SRT identical at PSA > 0.1 med. pre-SRT: 0.2ng/mL	> 0.4 or 2 at any time	7.8	10 yr.: 76% vs. 75% (p = 0.82 HR: 0.97)	OS: 87.6% vs. 87.4% (p = 0.92 HR: 0.98) FFDM: 93% vs. 90% (p = 0.095 HR:0.68)	SR urinary incontinence 1 yr.: 4.8 vs. 4 (p = 0.023) Urethral stricture grade 3/4 >2 yr.: 3% vs. 5% (p = 0.001)

GETUG-AFU 17 2020 [954]	424 target was 718 closed early	pT3a/pT3b/pT4a and SM+PSA post-RP: < 0.1ng/mL	66Gy (ART) vs. 66Gy early SRT at PSA 0.1 both groups: 6 mo. LHRH-A med. pre-SRT 0.24	> 0.4	6.25	5 yr.: 92% vs. 90% (p = 0.42)	n.r.	LT grade ≥ 2 GU: 27% vs. 7% (p < 0.001) ED: 28% vs. 8% (p < 0.001)
ARTISTIC 2020 [955]	2,153	see above	see above	see above	4.9-6.25	5 yr.: 89% vs. 88% (p = 0.7)	n.r.	n.r.

ART = adjuvant radiotherapy; BCR = biochemical recurrence; BPFS = biochemical progression-free survival; ED = erectile dysfunction; FFDM= Freedom from Distant Mets; FU = follow-up; fx = fraction; GU = genitourinary; LHRH = luteinising hormone-releasing hormone; LT = late toxicity; mo. = months; med = median; MFS = metastasis-free survival; n.r. = not reported; OS = overall survival; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiotherapy; SRT = salvage radiotherapy; + = positive; yr. = years.

6.3.5.e Adjuvant systemic therapy in N0 disease

The TAX3501 trial comparing the role of leuprolide (18 months) with and without docetaxel (six cycles) ended prematurely due to poor accrual. A phase III RCT comparing adjuvant docetaxel against surveillance after RP for locally advanced PCa showed that adjuvant docetaxel did not confer any oncological benefit [965]. Consequently, adjuvant chemotherapy after RP should only be considered in a clinical trial [966].

6.3.5.f Adjuvant treatment in pN1 disease

6.3.5.f.1 Adjuvant androgen ablation alone

The combination of RP and early adjuvant HT in pN+ PCa has been shown to achieve a 10-year CSS rate of 80% and has been shown to significantly improve CSS and OS in prospective RCTs [967, 968]. However, these trials included mostly patients with high-volume nodal disease and multiple adverse tumour characteristics, and these findings may not apply to men with less-extensive nodal metastases.

6.3.5.f.2 Adjuvant radiotherapy combined with ADT in pN1 disease

In a retrospective multicentre cohort study, maximal local control with RT to the prostatic fossa appeared to be beneficial in PCa patients with pN1 after RP, treated 'adjuvantly' with continuous ADT (within six months after surgery irrespective of PSA). The beneficial impact of adjuvant RT on survival in patients with pN1 PCa was highly influenced by tumour characteristics. Men with low-volume nodal disease (< 3 LNs), ISUP grade group 2–5 and pT3–4 or R1, as well as men with three to four positive nodes were more likely to benefit from RT after surgery, while the other subgroups did not [969]. In contrast, a retrospective multicentre study including 1,614 patients and a median follow-up of 7.02 years assessed ART + ADT. Adjuvant RT compared to SRT was associated with a decreased all-cause mortality and this reduction increased with each additional positive pelvic LN, from the first one on and the highest effect was for more than three positive nodes [970]. These data correspond with a United States National Cancer Database analysis based on 5,498 patients [971]. Another United States National Cancer Database study including 8,074 pN1 patients reports improved OS after ADT plus EBRT (including pelvic LNs) versus observation and versus ADT alone in all men with single or multiple adverse pathological features. Men without any adverse pathological features did not benefit from immediate adjuvant therapy [972].

In an SR of the literature, RT with or without ADT was associated with improved survival in men with locally advanced disease and a higher number of positive nodes [973]. Radiotherapy to the pelvic lymphatics and the prostate fossa plus long-term ADT can be offered to patients with pN1 disease [969, 974]. However, the optimal duration of ADT is still unknown.

6.3.5.f.3 Observation of pN1 patients after radical prostatectomy and extended lymph node dissection

Several retrospective studies and an SR addressed the management of patients with pN1 PCa at RP [945, 969, 973-975]. A subset of patients with limited nodal disease (1–2 positive LNs) showed favourable oncological outcomes and did not require additional treatment.

An analysis of 209 pN1 patients with one or two positive LNs at RP showed that 37% remained metastasis-free without need of salvage treatment at a median follow-up of 60.2 months [975]. Touijer *et al.*, reported their results of 369 pN1-positive patients (40 with and 329 without adjuvant treatment) and showed that higher pathologic grade group and > 3 positive LNs were significantly associated with an increased risk of BCR on

multivariable analysis [945]. Biochemical-free survival rates in pN1 patients without adjuvant treatment ranged from 43% at four years to 28% at ten years [973]. Reported CSS rates were 78% at five years and 72% at ten years. The majority of these patients were managed with initial observation after surgery, had favourable disease characteristics, and 63% had only one positive node [973]. Initial observation followed by early salvage treatment at the time of recurrence may represent a safe option in selected patients with a low disease burden [973].

6.3.5.g Recommendations for adjuvant treatment for pN0 and pN1 disease after radical prostatectomy*

Recommendations	Strength rating
Do not prescribe adjuvant androgen deprivation therapy (ADT) to pN0 patients.	Strong
In pN0 patients with ISUP GG 4–5 and pT3 ± positive margins, offer adjuvant intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT).	Weak
In pN1 patients, after an extended lymph node dissection (eLND), discuss three management options, based on nodal involvement characteristics: 1. Offer adjuvant ADT. 2. Offer adjuvant ADT with additional IMRT/VMAT plus IGRT. 3. Offer observation (expectant management) to a patient after eLND and ≤ 2 nodes and an undetectable PSA.	Weak

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

6.3.6 Persistent PSA after radical prostatectomy

6.3.6.a Definition of PSA persistence

Detectable PSA levels after RP may result from persistent local disease, pre-existing metastases, or residual benign prostate tissue. PSA persistence, defined as a PSA ≥ 0.1ng/mL within four to eight weeks of surgery, is observed in 5–20% of patients [976, 977]. However, timing of PSA measurement after RP might influence its interpretation [978, 979]. Among patients tested within three weeks of RP, 77% had PSA > 0.1ng/mL, but only 21% remained detectable on repeat testing. When PSA was measured more than five weeks after RP, only 10% had PSA > 0.1ng/mL, and 20% of these became undetectable on confirmatory testing [978]. Patients with preoperative PSA ≥ 20ng/mL are particularly prone to misclassification if tested too early, as delayed measurements (≥ 3 months) have shown that some of these patients eventually reach undetectable PSA levels [979].

6.3.6.b Predictors of PSA persistence after RP

A meta-analysis of consecutive patient cohorts reported that persistent PSA was more likely when risk factors such as high D'Amico risk, ISUP GG 4-5, pT stage ≥ 8 and presence of extraprostatic extension, seminal vesicle invasion, lymph node involvement and positive margin were present [980]. Cribriform pattern or intraductal carcinoma have also been associated with persistent PSA [981]. Moreover, an uptake in the pelvic nodes at PSMA PET represents one of the strongest predictors of persistently detectable PSA levels after surgery, with more than 50% of patients with miN1 PCa and more than two positive spots and/or extraprostatic extension experiencing PSA persistence [982, 983].

6.3.6.c Natural history of persistently elevated PSA after RP

Two SRs addressing persistent PSA confirmed a strong correlation of PSA persistence with poor oncologic outcomes [976, 977]. In a meta-analysis of retrospective cohorts, patients with persistent PSA (≥ 0.1 ng/mL) had worse BCR-free, metastasis-free and cancer-specific survival [980]. A retrospective study (n = 11,605) showed that persistent PSA is prognostic of an increased risk of metastasis and death [984]. At fifteen years post RP, MFS rates, OS and CSS rates were 53 versus 93% ($p < 0.001$), 65 versus 81% ($p < 0.001$) and 75 versus 96% ($p < 0.001$) for persistent versus undetectable PSA, respectively. In multivariable Cox regression models, persistent PSA represented an independent predictor for metastasis (HR: 3.59, $p < 0.001$), death (HR: 1.86, $p < 0.001$) and cancer-specific mortality (HR: 3.15, $p < 0.001$). However, not all patients with persistent PSA after RP experience disease recurrence. One study showed a 50% five-year BCR-free survival in men who had a persistent PSA level > 0.1 but ≤ 0.2ng/mL at six to eight weeks after RP [985]. Another study assessed the clinical outcome of 160 men with a persistently detectable PSA level after RP [986]. In multivariable analysis, the PSA slope ≥ 0.05 after RP (as calculated using PSA levels three to twelve months after surgery) and pathological ISUP grade group (≥ 3 vs. ≤ 2) were significantly associated with the development of distant metastases among patients with persistent PSA. Prostate-specific antigen slope is more commonly reported as PSA doubling time (calculated by log [PSA slope]) [987]. Increasing PSA levels are associated with a higher risk of PCa-specific

mortality particularly in patients with more aggressive disease [988]. Patients with persistent PSA levels ≥ 1 ng/ml had higher all-cause and PCa-specific mortality risk compared to those with PSA levels < 1 ng/mL [979].

6.3.6.d Imaging in patients with persistently elevated PSA after RP

Compared to conventional imaging, PSMA PET/CT is characterised by superior accuracy compared to conventional imaging. However, studies of patients with PSA persistence after RP are limited compared to those inclusive of patients with BCR with/without persistent PSA.

A study of 129 patients who had either persistent PSA (52%) or BCR (48%) after RP, showed that men with a persistent PSA had significantly more pelvic nodal involvement on PSMA PET/CT than those with an initially undetectable PSA [989]. When focusing on patients with PSA persistence a multicentre retrospective study included 191 patients with persistently elevated PSA after RP and ^{68}Ga-PSMA-PET/CT was positive in 68%, 35% of whom had disease confined to the pelvis (obturator, presacral/mesorectal most common) and 33% had distant metastases [525]. A subgroup analysis of 33 patients with pre- and post-RP imaging showed PET-persistence in 45%, new lesions in 24% and negative post-RP PET in 30%. Another retrospective study included 150 patients with persistent PSA after RARP who were restaged with both ^{68}Ga-PSMA and ^{18}F-DCFPyL PSMA. The authors found that, in the presence of persistent PSA, the majority of patients already had involved pelvic LNs (33%) or distant metastases (26%) that would support a role of PSMA PET/ CT imaging in guiding (salvage) treatment strategies [990].

Taken together, these findings support the role of PSMA PET/CT in identifying sites of residual or metastatic disease in patients with persistent PSA after RP, enabling the implementation of metastasis-directed therapies.

6.3.6.e Management options for patients with persistent PSA

6.3.6.e.1 Comparison with biochemical recurrence (BCR)

Persistent PSA after RP is clearly a poor prognostic indicator, likely representative of low volume synchronous metastatic disease rather than metachronous disease as in BCR. A retrospective analysis of the RTOG 9601 trial of SRT +/- ADT (bicalutamide) for biochemical failure after RP considered patients with persistent PSA (n = 90) or BCR (n = 670) as the cause for biochemical failure and showed higher 10-year metastatic progression rate (29% vs. 10%, p < 0.0001), higher 10-year overall mortality rate (25% vs. 12%, p = 0.03), and higher local progression rate (3.2% vs. 1.4%, p = 0.0001) [991]. In the ARO 96-02, a prospective RCT, 74 patients with PSA persistence (20%) received immediate SRT only (66Gy per protocol [arm C]). The 10-year clinical relapse-free survival was 63% and showed worse 10-year metastasis-free survival (67% vs 83%) and overall survival (68% vs 84%) than BCR patients [992]. Therefore, it is likely that outcomes are worse than for men with persistent PSA than those experiencing BCR [993]. Indeed, studies investigating PSA persistence were excluded from the EAU Guidelines Biochemical Recurrence risk groups [994].

6.3.6.e.2 Postoperative RT

The benefit of postoperative RT (adjuvant or salvage) in patients with persistent PSA remains unclear due to a lack of RCTs specifically focusing on this setting. AN SR reported that SRT was associated with improved survival outcomes, although the available evidence is of low quality and did not include patients restaged with PSMA/PET [977].

Another study compared oncological outcomes of patients with persistent PSA who received SRT vs. those who did not [984]. In the subgroup of patients with persistent PSA, after 1:1 propensity score matching between those treated with SRT versus no RT, 10-year overall- and cancer-specific survival rates were 87 versus 73% and 94 versus 82% (p < 0.01), respectively. These differences remained statistically significant when patients were stratified according to margin status, pathologic stage, ISUP GG, and lymph node involvement. In multivariable models SRT was associated with lower risk of death (HR: 0.42, p = 0.02) and lower cancer-specific death (HR: 0.29, p = 0.03). SRT dose was 46Gy for the 54% of patients with available data, but SRT field and ADT use was unavailable. A retrospective analysis of 313 patients with PSA persistence (median follow-up 4.5 years) suggested a benefit of SRT, with or without ADT, compared to no SRT in improving metastases-free (HR 0.39, p = 0.001), cancer-specific (HR 0.34, p = 0.03) and overall survival (HR 0.24, p = 0.001) [995]. These benefits were associated with higher incidence of bowel symptoms (34 vs. 19%, p = 0.01) and bothersome incontinence if given within six months of surgery (p < 0.001).

Poor oncological outcomes are driven by the level of pre-RT PSA, the presence of ISUP GG ≥ 4 in the RP histology and pT3b disease [988, 992, 996-999]. Two studies suggested that only men with a persistent PSA after RP and ISUP GG ≤ 3 benefit significantly [995, 1000], where positive margins, higher T stage, pN1 and lower ISUP GG were most likely to benefit from SRT, although this was not supported by Preisser *et al.* [984, 995].

The current data do not allow clear treatment recommendations.

6.3.6.e.3 Multimodal therapy (ADT with postoperative RT)

The RTOG 9601 trial randomised patients with either PSA persistence defined as PSA nadir after surgery > 0.5 ng/mL (n = 45, 12%) or BCR (n = 338, 88%) to 24 months of bicalutamide versus placebo during and after SRT [1001]. Although the study demonstrated a benefit of antiandrogen therapy in terms of OS at a median follow-up of 13 years, no subgroup analyses were performed focusing only on men with PSA persistence. Similarly, the NRG Oncology/RTOG 0534 SPPORT trial included patients with PSA persistence after prostatectomy, alongside those with rising PSA, and demonstrated improved freedom from progression with the addition of four to six months of ADT and pelvic lymph node radiotherapy [1002]. However, no subgroup analysis assessing patients with PSA persistence was reported. Other randomised trials which assessed the role of concomitant ADT and its duration at the time of SRT on oncologic control such as the RADICALS-HD and the GETUG-AFU 16 both excluded patients with PSA persistence and, therefore, their results are not applicable to this setting [1003, 1004].

The phase II GETUG-22 trial comparing RT (46Gy pelvis with 66Gy prostate bed boost) with RT plus short-term ADT for post-RP PSA persistence (0.2–2.0ng/mL) in 125 patients reported good tolerability of the combined treatment. The oncological endpoints are yet to be published [1005]. A multicentre, retrospective study from Japan considered 383 patients with pN1 and persistent PSA after RP and reported that the addition of SRT (median 66Gy; prostate bed with pelvis 67%, prostate bed alone 24%) to ADT showed better castration resistance-free (5-year $p < 0.001$, 10-year $p = 0.02$) and metastasis-free (5-year $p < 0.001$, 10-year $p = 0.15$), but not overall survival, than ADT alone in patients with pretreatment PSA ≥ 0.52ug/L [1006].

6.3.6.f Conclusion

The available data suggest that patients with PSA persistence after RP have worse outcomes and serve to benefit most from early aggressive multimodality treatment, however, the lack of prospective RCTs makes firm recommendations difficult.

6.3.6.g Recommendations for the management of persistent PSA after radical prostatectomy

Recommendations	Strength rating
Offer a prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT) scan to males with a persistent prostate-specific antigen (PSA) and rising if the results will influence subsequent treatment decisions.	Weak
Treat males with persistent PSA and no evidence of distant metastatic disease with salvage radiotherapy and additional hormonal therapy.	Weak

6.4 Management of PSA-only recurrence after treatment with curative intent

Follow-up will be addressed in Chapter 7 and is not discussed in this section.

6.4.1 Background

Between 27% and 53% of all patients undergoing RP or RT develop a rising PSA (PSA recurrence). Whilst metastatic progression is universally preceded by rising PSA levels, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily lead to clinically apparent metastatic disease. Physicians treating patients with PSA-only recurrence face a difficult set of decisions in attempting to delay the onset of metastatic disease and death while avoiding overtreating patients whose disease may never affect their OS or QoL. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.

6.4.1.a PSA velocity and doubling time

Various PSA kinetics definitions have been proposed with different methods of calculation (log transformed or not) and eligible PSAs:

- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year); and
- PSA doubling time (PSA-DT): measures the exponential increase in serum PSA over time.

Prostate-specific antigen velocity is easier to calculate by subtracting the initial value from the final value, dividing by time. However, by ignoring middle values, not all PSA values are accurately taken into account.

Prostate-specific antigen DT is calculated assuming an exponential rise in serum PSA. The formula takes into account the natural logarithm of two divided by the slope obtained from fitting a linear regression of the natural log of PSA over time [1007]. However, many different PSA-DT calculations have been assessed according to the mathematical formula used and to the included PSA values (number, time period, intervals) [1008]. The 'MSKCC' method, for example, calculates a regression slope integrating all PSA values. Other methods transform PSA before calculating the slope and do not include all PSA values (different time frames and minimal intervals) [1009]. O'Brien and colleagues identified more than 20 different definitions of PSAV and PSA-DT and demonstrated that obtained values could vary widely between definitions [1009].

However, some rules can be considered for PSA-DT calculation [1007]:

- At least three PSA measurements are required.
- A minimum period between measurements (four weeks) is preferable due to potential statistical 'noise' when PSA values are obtained too close together (this statement can be reconsidered in case of highly active disease).
- All included PSA values should be obtained within the past twelve months at most, to reflect the current disease activity.
- PSA-DT is often expressed in months, or in weeks in highly active disease.

These measurements do not provide additional information compared with PSA alone [604, 1009-1011]. In the post-local therapy relapse setting, PSA-DT has been correlated with distant progression and with poorer outcomes after salvage treatments [1012, 1013]. Prostate-specific antigen DT has been linked with metastasis-free and OS in non-metastatic CRPC (nmCRPC) and identifies patients with high-risk nmCRPC who benefit from intensified therapy (PSA-DT threshold < ten months) [1014].

*6.4.2 **Controversies in the definitions of clinically relevant PSA relapse***

The PSA level that defines treatment failure depends on the primary treatment. Patients with rising PSA after RP or primary RT have different risks of subsequent symptomatic metastatic disease based on various parameters, including the PSA level. Therefore, physicians should carefully interpret BCR endpoints when comparing treatments. Clinicians should interpret a PSA rise bearing in mind the EAU BCR risk groups [994].

After RP, the threshold that best predicts further metastases is a PSA > 0.4ng/mL and rising [1015]. However, with access to ultrasensitive PSA testing, a rising PSA much below this level will be a cause for concern for patients.

After primary RT - with or without short-term hormonal manipulation - the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure (with an accuracy of > 80% for clinical failure) is 'any PSA increase > 2ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir' [1016].

After HIFU or cryotherapy, no endpoints have been validated against clinical progression or survival. Therefore, it is not possible to offer a firm recommendation of an acceptable PSA threshold after these alternative local treatments [994].

*6.4.3 **Natural history of biochemical recurrence***

Once a PSA recurrence has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites. A SR and meta-analysis investigated the impact of BCR on clinical endpoints and concluded that patients experiencing BCR are at an increased risk of developing distant metastases, as well as PCa-specific and overall mortality [994]. The effect size of BCR as a risk factor for mortality, however, is highly variable. After primary RP, its impact ranges from HR 1.03 (95% CI: 1.004–1.06) to HR 2.32 (95% CI: 1.45–3.71) [1017, 1018]. After primary RT, OS rates are approximately 20% lower at eight to ten years follow-up, even in men with minimal comorbidity [1019, 1020]. Still, the variability in reported effect sizes of BCR remains high and suggests that only certain patient subgroups with BCR might be at an increased risk of mortality.

The risk of subsequent metastases, PCa-specific and overall mortality may be predicted by the initial clinical and pathologic factors (e.g. T category, PSA, ISUP grade group) and PSA kinetics (PSA-DT and interval to PSA failure), which was further investigated by the SR [994].

For patients with BCR after RP, the following outcomes were found to be associated with significant prognostic factors, including:

- distant metastatic recurrence: positive surgical margins, high RP specimen pathological ISUP GG, high pT category, short PSA-DT, high pre-SRT PSA;

- prostate-cancer-specific mortality: high RP specimen pathological ISUP grade group, short interval to biochemical failure as defined by investigators, short PSA-DT; and
- overall mortality: high RP specimen pathological ISUP grade group, short interval to biochemical failure, high PSA-DT.

For patients with BCR after RT, the corresponding outcomes are:
- distant metastatic recurrence: high biopsy ISUP grade group, high cT category, short interval to biochemical failure;
- prostate-cancer-specific mortality: short interval to biochemical failure; and
- overall mortality: high age, high biopsy ISUP grade group, short interval to biochemical failure, high initial (pretreatment) PSA.

Based on this meta-analysis, the proposal is to stratify patients into two risk categories since not all patients with BCR will have similar outcomes (see Table 6.4.1). The stratification into 'EAU Low-Risk' or 'EAU High-Risk' BCR after RP has been validated in a European cohort [1021].

Table 6.4.1: EAU risk categories for patients developing biochemical recurrence

	EAU Low Risk BCR	EAU High Risk BCR
After RP	PSA-DT > 1 yr AND pathological ISUP grade group < 4	PSA-DT ≤ 1 yr OR pathological ISUP grade group 4-5
After RT	interval to biochemical failure > 18 mo. AND biopsy ISUP grade group < 4	interval to biochemical failure ≤ 18 mo OR biopsy ISUP grade group 4-5

6.4.4 The role of imaging in PSA-only recurrence

Imaging is only of value if it leads to a treatment change that results in an improved outcome. In practice, however, very limited data are available regarding the outcome's consequent on imaging at recurrence.

6.4.4.a Assessment of metastases (including nodal)

6.4.4.a.1 Bone scan and abdominopelvic CT

As BCR after RP or RT precedes clinical metastases by seven to eight years on average [939, 1022], the diagnostic yield of conventional imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients [1023]. In men with PSA-only recurrence after RP, the probability of a positive bone scan is < 5% when the PSA level is < 7ng/mL [1024, 1025]. Only 11–14% of patients with BCR after RP have a positive CT [1024]. In a series of 132 men with BCR after RP, the mean PSA level and PSA velocity associated with a positive CT were 27.4ng/mL and 1.8ng/mL/month, respectively [1026].

6.4.4.a.2 Fluoride PET/CT

^{18}F-NaF PET/CT has a higher sensitivity than bone scan in detecting bone metastases [1027]. However, ^{18}F-NaF PET/CT is limited by a relative lack of specificity and by the fact that it does not assess soft-tissue metastases [1028].

6.4.4.a.3 Prostate-specific membrane antigen hybrid imaging

Radiolabelled PSMA hybrid imaging (i.e., PET/CT or PET-MRI) has shown good potential in patients with BCR. The diagnostic performance of radiolabelled PSMA PET/CT in patients with BCR has been investigated in several SRs and meta-analyses. The pooled sensitivity, specificity and AUC values for ^{18}F-PSMA PET/CT in the diagnosis of prostate recurrence and/or metastasis were 0.93 (0.89–0.95), 0.94 (0.85–0.98) and 0.96 (0,94–0.98), respectively. The per-patient pooled sensitivity and specificity values were 0.92 (0.86–0.96) and 0.83 (0.41–0.97), respectively. The per-lesion pooled sensitivity and specificity values were identical: 0.91 (0.86–0.94) [1029]. The positivity rate increases with PSA, from 48% at PSA of 0.2-0.5 ng/ml to >90% at PSA >2 ml [1030].

A prospective multicentre, multi-reader, open-label, phase II/III trial (OSPREY) evaluated the diagnostic performance of ^{18}F-DCFPyL in patients with presumptive radiologic evidence of recurrent or metastatic PCa on conventional imaging [964]. Median sensitivity and median PPV were 95.8% (95% CI: 87.8%–99.0%) and 81.9% (95% CI: 73.7%–90.2%), respectively.

Another prospective study evaluated the diagnostic performance of ^{18}F-DCFPyL in 208 men with BCR after RP or RT. The primary endpoint, the correct localisation rate was achieved, demonstrating positive findings on ^{18}F-DCFPyL PET/CT in the setting of negative standard conventional imaging [1031]. At present, there are no conclusive data concerning the comparison of such tracers [1032].

6.4.4.a.4 Whole-body and axial MRI

Whole-body MRI has not been widely evaluated in BCR because of its limited value in the detection of early metastatic involvement in normal-sized LNs [516, 551, 1033]. In a prospective series of 68 patients with BCR, the diagnostic performance of DW-MRI was significantly lower than that of ^{68}Ga-PSMA PET/CT and ^{18}NaF PET/CT for diagnosing bone metastases [1034].

6.4.4.b Assessment of local recurrences

6.4.4.b.1 Local recurrence after radical prostatectomy

As the sensitivity of anastomotic biopsies is low, particularly for PSA levels < 1ng/mL [1023], SRT is usually decided based on BCR without histological proof of local recurrence.

Magnetic resonance imaging can detect local recurrences in the prostatic bed. The PSA threshold for MRI positivity appears to be between 0.3 and 0.5ng/mL, and PSA kinetics also influence the MRI positivity, even at low PSA values [1035]. Two single-centre studies found that a negative MRI was an independent predictor of failure of SRT [1036, 1037]. Conversely, a small (≤ 0.4cc) relapse located at the vesico-urethral anastomosis is associated with excellent prognosis at salvage RT [1038]. The Prostate Imaging for Recurrence Reporting (PI-RR) system has been recently launched to standardise MRI interpretation in the context of BCR after RP or RT [1039]. Initial assessment suggests good reproducibility of the score [1040, 1041].

The detection rates of ^{68}Ga-PSMA PET/CT in patients with BCR after RP increase with the PSA level [1042]. PSMA PET/CT studies showed that a substantial part of recurrences after RP were located outside the prostatic fossa, even at low PSA levels [1043, 1044]. Combining ^{68}Ga-PSMA PET and MRI may improve the detection of local recurrences as compared to ^{68}Ga-PSMA PET/CT alone [1045-1047].

6.4.4.b.2 Local recurrence after radiation therapy

In patients with BCR after RT, biopsy status is a major predictor of outcome, provided the biopsies are obtained at least 24 months after initial treatment. Given the morbidity of local salvage options, histological proof of the local recurrence must be obtained before treating the patient [1023].

Magnetic resonance imaging has yielded excellent results in identifying local recurrence and can be used for biopsy targeting and guiding local salvage treatment [1023, 1048, 1049], even if it slightly underestimates the volume of the local recurrence [1050]. Prostate-specific membrane antigen PET/CT can also detect local recurrences after RT [1051] and concordance between PSMA PET/CT and MRI is highly suggestive of cancer recurrence [1052].

In the FLAME trial PSMA PET/CT was used for recurrence after RT. Intra-prostatic recurrences in intermediate- and high-risk patients appeared at the location of the primary tumour in 98% of cases [1053].

6.4.4.c Summary of evidence of imaging in case of biochemical recurrence

In patients with BCR, imaging can detect both local recurrences and distant metastases, however, the sensitivity of detection depends on the PSA level. After RP, PSMA hybrid imaging is the modality with the highest sensitivity at low PSA levels (< 0.5ng/mL) and may help distinguishing patients with recurrences confined to the prostatic fossa from those with distant metastases, which may impact the design and use of post-RP SRT. After RT, MRI has shown excellent results at detecting local recurrences and guiding prostate biopsy. Given the substantial morbidity of post-RT local salvage treatments, distant metastases must be ruled out in patients with local recurrences and who are fit for these salvage therapies.

6.4.4.d Recommendations for imaging in patients with biochemical recurrence

Recommendations	Strength rating
Prostate-specific antigen (PSA) recurrence after radical prostatectomy	
Perform prostate-specific membrane antigen (PSMA) positron emission tomography/ computed tomography (PET/CT) if the PSA level is > 0.2 ng/mL and if the results will influence subsequent treatment decisions (i.e. EAU BCR risk groups).	Weak

PSA recurrence after radiotherapy	
Perform PSMA PET/CT in patients fit for curative salvage treatment.	Strong
Perform prostate magnetic resonance imaging to localise abnormal areas and guide biopsies in patients fit for local salvage therapy.	Weak

6.4.5 Treatment of PSA-only recurrences

The timing and treatment modality for PSA-only recurrences after RP or RT remain a matter of controversy based on the limited evidence.

6.4.5.a Treatment of PSA-only recurrences after radical prostatectomy

6.4.5.a.1 Salvage radiotherapy for PSA-only recurrence after radical prostatectomy (pTxcN0M0, without PET/CT)

Early SRT provides the possibility of cure for patients with an increasing PSA after RP. Boorjian *et al.* reported a 75% reduced risk of systemic progression with SRT when comparing 856 SRT patients with 1,801 non-SRT patients [1054]. The RAVES and RADICALS trials assessing SRT in post-RP patients with PSA levels exceeding 0.1–0.2ng/mL showed five-year freedom from BCR and BCR-free survival rates of 88% [1067, 1055]. Tilki *et al.* demonstrated the results of a matched-pair analysis of 1,832 patients with BCR: 32.9% (n = 603) received SRT without ADT, while 1,229 (67.1%) had an observational strategy. The median follow-up was 95.9 months. Median total SRT dose was 70.2Gy. After 1:1 propensity score matching, at fifteen years after RP, MFS and OS rates were 84.3 versus 76.9% ($p < 0.001$) and 85.3 versus 74.4% ($p = 0.04$) for SRT and no RT, respectively [1056].

The PSA level at BCR was shown to be prognostic [1054]. More than 60% of patients who are treated before their PSA level rises to > 0.5ng/mL will achieve an undetectable PSA level [1057-1059], corresponding to an approximate 80% chance of being progression-free five years later [1060]. A retrospective analysis of 635 patients who were followed after RP and experienced BCR and/or local recurrence and either received no salvage treatment (n = 397) or SRT alone (n = 160) within two years of BCR showed that SRT was associated with a threefold increase in PCa-specific survival relative to those who received no salvage treatment ($p < 0.001$). Salvage RT has been shown to be effective mainly in patients with a short PSA-DT [1061].

In a retrospective multicentre study including 25,551 patients with at most one high-risk factor after RP (ISUP GG 4-5 or pT3/4), initiating SRT above a PSA level of 0.25 ng/mL was associated with increased ACM risk. After a median follow-up of six years, patients who received sRT at a PSA level > 0.25 ng/mL had a significantly higher ACM risk (AHR, 1.49; 95% CI, 1.11 to 2.00; $p = 0.008$) compared with men who received sRT when the PSA was ≤ 0.25 mg/mL [1062]. For an overview of SRT, see Table 6.4.3.

Although biochemical progression is now widely accepted as a surrogate marker of PCa recurrence, metastatic disease, disease-specific and OS are more meaningful endpoints to support clinical decision-making. A SR and meta-analysis on the impact of BCR after RP reports SRT to be favourable for OS and PCSM. SRT in particular should be initiated in patients with rapid PSA kinetics after RP and with a PSA cut-off of 0.4ng/mL [994]. An international multi-institutional analysis of pooled data from RCTs has suggested that MFS is the most valid surrogate endpoint with respect to impact on OS [1063, 1064]. Table 6.4.4 summarises the results of recent studies on clinical endpoints after SRT.

The EAU BCR definitions have been externally validated and may be helpful for individualised treatment decisions [994, 1021]. For men with limited life expectancy, salvage options are not indicated. A 'wait and see'strategy is an option for the EAU BCR 'Low-Risk' group [994, 1021].

6.4.5.a.2 Salvage radiotherapy combined with androgen deprivation therapy (pTxcN0, without PET/CT)

Data from RTOG 9601 suggest that both CSS and OS benefit when adding two years of bicalutamide (150 mg o.d.) to SRT [1001]. The OS benefit improved at 18 years (median follow up for surviving patients 18.9 years) to 53% for the combination treated patients (95% CI, 47%-58%) versus 43% (95% CI, 38%-49%) compared with 5% at 12 years. This improvement was also consistent with the initial report, with reduced incidence of metastatic PCs and PCa death for RT+HT [1065]. According to GETUG-AFU 16, six months of treatment with an LHRH-analogue can also significantly improve 10-year BCR, biochemical PFS and, modestly, MFS. However, SRT combined with either goserelin or placebo showed similar DSS and OS rates [1004].

In addition, Pollack *et al.*, reported on the results of a randomised three-arm phase III trial (NRG Oncology/RTOG 0534 SPPORT), adding six months' treatment with an LHRH analogue to SRT of the prostate bed (PBRT) (group 2) compared with PBRT alone (group 1) or the former combination with PBRT-RT and pelvic LN RT (PLNRT)

(group 3) [1002]. The primary endpoint was freedom from progression (FFP) after five years. However, using the Phoenix definition of biochemical progression (nadir + 2ng/mL used for definitive RT) and not the criterion of nadir + 0.2 as is commonly used (but without clear evidence) will have resulted in a later diagnosis of progression in the SPPORT trial.

With a median follow-up of 8.2 years of the surviving patients, FFP increased significantly for group 3 (87.4%) compared with group 2 (81.3%) ($p = 0.0027$) and group 1 (70.9%) ($p < 0.0001$) [1002]. The difference between group 2 and group 1 was also significant ($p < 0.0001$). Distant metastasis incidence rates (secondary endpoint) were lowest in group 3 (including RT of the pelvic lymphatics) and were significantly lower compared only with group 1 (PBRT only, HR: 0.52), similar to the rate of PCa deaths (HR: 0.51). No significant difference was seen for OS. A significantly higher risk of both acute and late side effects was identified in group 3. Therefore, the role of additional PLNRT remains unclear and should be further proven in RCTs including PSMA PET-CT [1066].

RADICALS HD investigated the role of RT without ADT (n = 737) versus RT plus six months of ADT (n = 747) and RT plus six months of ADT (n = 761) versus RT plus 24 months' long-term ADT (n = 762) in both the salvage and adjuvant settings [1003, 1067, 1068]. The design of RADICALS HD was complex and included components of the RADICALS RT trial together with the RADICALS HD component. RADICALS RT was a phase III comparison of ART versus observation and early SRT and has been published previously [956] (see Table 6.3.5.2).

RADICALS HD included men after prostatectomy (indications for ART or early SRT), median pre-SRT-PSA was 0.2ng/ml with conventional staging imaging (M0) without PET-CT. Due to the complex design, some patients were enrolled in a three-way randomisation (including patients from RADICALS RT, n = 492) and in a two-way randomisation (SRT + 6 months or 24 months of ADT, n = 1,197). The randomisation was influenced by physician preference. For this reason, more patients had high-risk factors in the short-term ADT versus long-term ADT study (ISUP >3: 29% versus 11% and for > pT3B tumours: 31% vs. 17%) compared with the no ADT and the short-term ADT study [1069].

With a median FU of nine years, the ten-year MFS (primary endpoint, inclusion of deaths from PCa only) for no ADT versus short-term ADT showed no significant difference for both arms (88.1% vs. 89.9%, $p > 0.05$) but for 'Clinical progression free survival' (68.3% vs. 79.4%, $p < 0.0001$ with some evidence of unproportional hazards) and '10-year freedom from non-protocol ADT' (73.3% vs. 82.3%, $p< 0.0001$, but with clear evidence of unproportional hazards). Maximum GU-Tox grade 3 was 16% (no ADT) versus 13% (short term ADT) ($p > 0.05$). With a median FU of 8.9 years, the 10-year MFS (primary endpoint) in the second randomisation showed a moderate significant difference (78.1% vs. 71.9%) in favour of the long-term ADT arm compared with the short-term ADT arm ($p = 0.029$, HR 0.773). Comparable significant differences were seen for 'Clinical progression-free survival' and for '10-year freedom from non-protocol ADT'. Maximum GU-Toxicity grade 3 was 14% (short-term ADT) versus 20% (long-term ADT).

The authors concluded that the findings for short-term ADT versus no ADT do not support the use of ADT in this patient population. For the comparison of long-term ADT versus short-term ADT, the conclusion was that 'individuals who can accept the additional duration of adverse effects, long-course ADT should be offered' with SRT.

The duration of androgen suppression with postoperative radiotherapy for non-metastatic PCa was analysed in an SR and meta-analysis [1070] from the DADSPORT group. The SR included five RCTs with 4,411 patients, the median follow up across the trials was 6.2 - 13 years, the primary endpoint was OS, secondary endpoints were MFS and PCSS. Overall survival was slightly improved with an absolute effect of 2% at eight years (HR: 0.86 CI: 0.74-1.00, $p = 0.057$) with no clear effect of duration of HT ($p = 0.6$). There was no evidence of a significant difference in OS between short- and long-course HT. The study noted that any benefit appeared to be confined to man with higher pre-SRT PSA levels ($p = 0.07$) and CAPRA-S scores ($p = 0.09$). Hormonal therapy improved MFS (HR 0.78, CI 0.69-0.88, $p < 0.001$) and PCSS (HR: 0.61, CI: 0.47-0.79, $p < 0.001$) with an absolute improvement of 4% in both groups after eight years. Post-hoc comparisons were not done for combinations of risk factors such as ISUP GG 4-5 and pT3. Only 247/ 679 patients (5.8% of total patients) were classified as dying from PCa clearly showing that the majority of patients had favourable prognostic tumours. In summary the SR concluded that the improvements of short- or long course HT in these patients are unlikely to be clinically meaningful and might be limited to people with higher-risk factors and should be balanced against the potential impact of long-term HT side effects on QoL.

One of these RCTs reports improved OS (RTOG 96-01), another (GETUG-AFU 16) moderately improved MFS (7%) at ten years. The two arm comparison (SRT versus SRT + 6 months ADT) of RADICALS HD did not improve MFS at ten years, this is in contrast to the results of the GETUG-AFU 16 trial. Only the comparison of SRT + 6 months ADT versus SRT + 24 months ADT of RADICALS HD moderately improved ten year MFS (6.2%). This improvement came with the cost of increased side effects of the additional 18 months ADT including a doubling of patients with testosterone suppression after ten years compared with six months of ADT [1071].

Table 6.4.5 provides an overview of these RCTs.

Due to methodological discrepancies and also related to follow-up and risk, it is, as yet, not evident which patients should receive ADT, which type of ADT, and for how long. Men at high risk of further progression (e.g. with a PSA ≥ 0.7ng/mL and GS ≥ 8) may benefit from SRT combined with two years of ADT. For those at lower risk (e.g. PSA < 0.7ng/mL and GS = 8), SRT combined with six months of ADT may be sufficient [1001]. Men with a low risk profile (PSA < 0.5ng/mL and GS < 8) and a PSA level < 0.5ng/mL may receive SRT alone. In an unplanned subgroup analysis [1072] (RTOG 96-01) of men with a PSA of 0.61 to 1.5 (n = 253), an OS benefit was associated with antiandrogen assignment (HR: 0.61, 95% CI: 0.39–0.94) [1072]. In those receiving early SRT (PSA < 0.6ng/mL, n = 389), there was no improvement in OS (HR: 1.16, 95% CI: 0.79–1.70), with increased other-cause mortality (sub-distribution HR: 1.94, 95% CI: 1.17–3.20, p = 0.01) and increased odds of late grades 3–5 cardiac and neurologic toxic side effects (OR: 3.57, 95% CI: 1.09–15.97, p = 0.05). These results suggest that pre-SRT PSA level may be a prognostic biomarker for outcomes of antiandrogen treatment with SRT.

An SR addressing the benefit from combining HT with SRT suggested risk stratification of patients based on the pre-SRT PSA (< 0.5, 0.6–1, > 1ng/mL), margin status and ISUP GG as a framework to individualise treatment [1073]. In addition, potential risk factors that should be considered are (short) PSA-doubling time and pT3b-4 tumours [957, 958, 1067-1069].). If PSMA-PET was used for staging, this discussion is restricted to patients with a negative or cN0 PSMA-PET-CT. For patients with cN1 in PSMA-PET-CT see Section 6.4.5.a.2.c.

In conclusion, regarding the 'weak' recommendation 'offer hormonal therapy in addition to SRT to men with BCR', we have different results of three RCTs for additional short-term ADT (six months) to SRT. One of the RCTs showed an increase of MFS [1004], while the second and third RCTs did not [1002, 1068]. Of two RCTs with long-term ADT in addition to SRT, one RCT showed a significant better OS [1001] while the second did not [1068], but this second RCT showed a moderate increase in MFS, at the cost of a higher rate of severe side effects. Additionally, in RADICALS HD, no subgroup analysis of risk factors was carried out. These conclusions were supported by the DADSPORT meta-analysis [1070]. There is a suggestion that absolute benefits of HT vary by prognostic risk and the number of prognostic risk factors in individual patients, especially in an early salvage setting (PSA ≤ 0.5 ng/mlL. The potential for a greater benefit of long- over short-course ADT seems to be small and must be weighed against increased toxicity and reduced QoL.

6.4.5.a.2.a Target volume, dose, toxicity

Various attempts have been made to define common outlines for 'clinical target volumes' for pN0 PCa [1074, 1075] and for organs at risk of normal tissue complications [1074]. However, given the variations of techniques and dose constraints, a satisfactory consensus has not yet been achieved. A benefit in biochemical PFS, but not MFS, has been reported in patients receiving whole-pelvis SRT (± ADT), but the advantages must be weighed against possible side effects [1066]. This is supported by data from the SPPORT Trial (NRG Oncology/RTOG 0534 SPPORT), but it remains controversial [1002].

The optimal SRT dose has not been well defined, but should be at least 64Gy to the prostatic fossa (± the base of the SVs, depending on the pathological stage after RP) [961, 1076]. In an SR, the pre-SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that the treatment dose above 70Gy should be administered at the lowest possible PSA level [1077]. The combination of pT stage, margin status and ISUP grade group and the PSA at SRT seems to define the risk of biochemical progression, metastasis and overall mortality [949, 1078]. In a study of 894 node-negative PCa patients, doses ranging from 64 to > 74 Gy were assigned to twelve risk groups defined by their pre-SRT PSA classes < 0.1, 0.1–0.2, 0.2–0.4, and > 0.4 ng/mL and ISUP grade group < 1 versus 2/3 versus > 4 [1079]. The updated Stephenson nomograms incorporate the SRT and ADT doses as predictive factors for biochemical failure and distant metastasis [1080].

Two RCTs have been published (as shown in Table 6.4.6). Intensity-modulated radiation therapy plus IGRT was used in 57% of the patients in the SAKK trial [1081] and in all patients of a Chinese trial [1082]. No patient had a PSMA PET/CT before randomisation. The primary endpoint in both trials was 'freedom from biochemical

progression', which was not significantly improved with higher doses. In the Chinese trial, however, a subgroup analysis showed a significant improvement of this endpoint for patients with Gleason 8-10 tumours (66.5% vs. 30.2%, p = 0.012) and for multiple positive surgical margins (82.5% vs. 57.5%, p = 0.037) [1082]. In this trial, patients were treated with ART or SRT and the number of patients was relatively small (n = 144). At this time, it seems difficult to draw final conclusions about the optimal total RT dose and longer follow-up should be awaited, but subgroups of high-risk patients might benefit from higher total doses.

In contrast to definitive RT with moderate and extreme hypofractionated RT as additional standard procedures, normofractionation (single dose 1.8 Gy-2 Gy) remains the standard of care in the SRT-setting. In the randomised NRG-GU-003 phase III (HYPORT) trial 296 patients with a detectable PSA (≥ 0.1 ng/mL) with pT2/3 cN0 disease or an undetectable PSA (< 0.1 ng/mL) with pT3 or pT2 SM+ were randomised to receive 62.5 Gy in 25 fractions (HYPORT) or 66.6 Gy in 37 fractions (COPORT) [784]. The co-primary endpoints were the two-year change baseline scores for the bowel and urinary domains of the EPIC questionnaire. Median follow up was 2.1 years. The mean GI change scores for HYPORT and COPORT were both clinically significant and different in statistical significance at the end of RT (-15.52 and -7.06, p < 0.001) but were resolved at six and twelve months. There was no significant difference for biochemical failure. The trial concluded that HYPORT should be standard practice for patients receiving SRT. In addition, a retrospective study of 161 patients treated with HYPORT (a total dose of 65 Gy compared with 62.5 Gy in the RCT [1083]), with a median follow up of 106 months, reported 2% grade 3 GU-toxicities. However, 44 (27.3%) patients experienced 58 grade 3-5 complications, of which 55 were GU-related. Longer follow-up is required before a new standard of care for SRT can be defined in this setting.

Salvage RT is associated with toxicity. In one report on 464 SRT patients receiving a median 66.6 (maximum 72) Gy, acute grade 2 toxicity was recorded in 4.7% for both the GI and GU tract. Two men had late grade 3 reactions of the GI tract, but overall, severe GU tract toxicity was not observed. Late grade 2 complications occurred in 4.7% (GI tract) and 4.1% (GU tract), respectively, and 4.5% of the patients developed moderate urethral stricture [1084].

In an RCT on dose escalation for SRT (n = 350), acute grade 2 and 3 GU toxicity was observed in 13.0% and 0.6%, respectively, with 64Gy and in 16.6% and 1.7%, respectively, with 70Gy. Gastrointestinal tract grades 2 and 3 toxicity occurred in 16.0% and 0.6%, respectively, with 64Gy, and in 15.4% and 2.3%, respectively, with 70Gy [1085, 1086]. Late grade 2 and 3 GI toxicity was significantly increased with higher doses but without significant differences in QoL. In this study, however, the rectal wall dose constraints were rather permissive and in 44% of the patients outdated 3-D techniques were used [1081].

With dose escalation over 72Gy and/or up to a median of 76Gy, the rate of severe side effects, especially GU symptoms, clearly increases, even with newer planning and treatment techniques [1087, 1088]. In particular, when compared with 3D-CRT, IMRT was associated with a reduction in grade 2 GI toxicity from 10.2 to 1.9% (p = 0.02), but no effect on the relatively high level of GU toxicity was shown (5-year, 3D-CRT 15.8% vs. IMRT 16.8%) [1087]. However, in a RCT comparing 66Gy and 72Gy with all patients having IMRT plus IGRT (n = 144), no significant differences for GI and GU-toxicity were demonstrated [1089]. After a median salvage IMRT dose of 76Gy, however, the five-year risk of grade 2–3 toxicity rose to 22% for GU and 8% for GI symptoms, respectively [1088]. Doses of at least 64Gy and up to 72Gy in patients without PET/CT can be recommended [1084, 1085].

Table 6.4.3: Selected studies of post-prostatectomy salvage radiotherapy, stratified by pre-salvage radiotherapy PSA level* (pTxcN0M0, without PET/CT)

Study	n	Median FU (mo)	pre-SRT PSA (ng/mL) median	RT dose ADT	bNED/PFS (year)	5-yr. results
Bartkowiak, *et al.* 2018 [1084]	464	71	0.31	66.6Gy	54% (5.9)	73% vs. 56%; PSA < 0.2 vs. ≥ 0.2ng/mLp < 0.0001
Stish, *et al.* 2016 [1057]	1,106	107	0.6	68Gy 16% ADT	50% (5) 36% (10)	44% vs. 58%; PSA ≤ 0.5 vs. > 0.5ng/mL p < 0.001

Tendulkar, *et al.* 2016 [1080]	2,460	60	0.5	66Gy 16% ADT	56% (5)	Pre-SRT PSA 71% 0.01–0.2ng/mL 63% 0.21–0.5ng/mL 54% 0.51–1.0ng/mL 43% 1.01–2.0ng/mL 37% > 2.0ng/mL p < 0.001
Tilki, *et al.* 2023 [1062]	25,551 SRT at: PSA < 0.25 n = 1,556 PSA > 0.25 n = 1,677 No RT: n = 21,645	72	Not given	Med. 68.4Gy SRT+ADT: 1,489 ART: n = 673 ADT: 208	Not given	ACM (six years): HR 1.49 of higher risk when SRT at start was > 0.25 (p = 0.008)

**Androgen deprivation therapy can influence the outcome 'biochemically no evidence of disease (bNED)' or 'progression-free survival.' To facilitate comparisons, 5-year bNED/PFS read-outs from Kaplan-Meier plots are included.*

ADT = androgen deprivation therapy; bNED = biochemically no evidence of disease; FU = follow up; mo. = months; n = number of patients; PFS = progression-free survival; PSA = prostate-specific antigen; RT = radiotherapy; SRT = salvage radiotherapy.

Table 6.4.4: Selected studies reporting clinical endpoints after SRT (cTxcN0M0, without PET/CT)
(the majority of included patients did not receive ADT)

Study	n	Median FU (mo)	Regimen	Outcome	
Bartkowiak, *et al.* 2018 [1084]	464	71	66.6 (59.4-72) Gy no ADT	5.9 yr. OS post-SRT PSA < 0.1ng/mL 98% post-SRT PSA ≥ 0.1ng/mL 92% p = 0.005	
Jackson, *et al.* 2014 [1090]	448	64	68.4Gy no ADT	5 yr. DM post-SRT PSA < 0.1ng/mL 5% post-SRT PSA ≥ 0.1ng/mL 29% p < 0.0001 5 yr. DSM post-SRT PSA < 0.1ng/mL 2% post-SRT PSA ≥ 0.1ng/mL 7% p < 0.0001	OS post-SRT PSA < 0.1ng/mL 97% post-SRT PSA ≥ 0.1ng/mL 90% p < 0.0001
Stish, *et al.* 2016 [1057]	1,106	107	68 (64.8-70.2) Gy 39% 2D treatment planning incl. 16% ADT	5 and 8.9 yr. DM SRT: PSA ≤ 0.5ng/mL 7% and 12% SRT: PSA > 0.5ng/mL 14% and 23% p < 0.001 5 and 8.9 yr. DSM SRT: PSA ≤ 0.5ng/mL < 1% and 6% SRT: PSA > 0.5ng/mL 5% and 10% p = 0.02 5	8.9 yr. OS SRT: PSA ≤ 0.5ng/mL 94% and 86% SRT: PSA > 0.5ng/mL 91% and 78% p = 0.14
Tendulkar, *et al.* 2016 [1080]	2,460	60	66 (64.8-68.4) Gy incl. 16% ADT	10-yr. DM (19% all patients) Pre-SRT PSA 9% 0.01–0.2ng/mL; 15% 0.21–0.5ng/mL; 19% 0.51–1.0ng/mL; 20% 1.01–2.0ng/mL; 37% > 2.0ng/mL p < 0.001	

ADT = androgen deprivation therapy; DM = distant metastasis; DSM = disease specific mortality; FU = follow up; mo. = months; n = number of patients; OS = overall survival; PSA = prostate specific antigen; SRT = salvage radiotherapy; yr. = years.

Table 6.4.5: Randomised controlled trials comparing salvage radiotherapy combined with androgen deprivation therapy vs. salvage radiotherapy alone

Study	n	Risk groups	Median FU (mo)	Regimen	Outcome	
GETUG-AFU 16 2019 [1004]	369 SRT + ADT 374 RT	ISUP GG ≤ 2/3 89% SUP GG ≥ 4 11% cN0	112	66Gy PBRT+ 6 mo. LHRH analogue 66Gy PBRT	10 yr. PFS: RT + ADT, 64% PFS: RT, 49% p < 0.0001	MFS: RT + ADT, 75% MFS: RT, 69% p = 0.034
RTOG 9601 2017 [1001]	384 SRT + ADT 376 SRT	pT2 R1, pT3 cN0	156	64.8Gy PBRT + bicalutamide 24 mo. 64.8Gy PBRT + placebo	12 yr. cumulative DM RT + ADT: 14% RT + placebo: 23% p = 0.005 OS RT + ADT: 76% RT + placebo: 71% p = 0.04	DSM RT + ADT: 5.8% RT + placebo: 13.4% p < 0.001
NRG Oncology/ RTOG 0534 SPPORT [1002]	564 SRT 578 SRT + ADT 574 SRT + PBRT + ADT	pT2 or pT3 ISUP GG <5 Pre SRT PSA: 0.1-2.0	survivors: 8.2 years	64.8–0.2Gy PBRT 64.8–70.2Gy PBRT 6 mo. LHRH analogue 64.8–70.2Gy PBRT + 45Gy PLNRT 6 mo. LHRH analogue	5 yr. FFP (primary endpoint) 70.9% Group 1 81.3% Group 2 87.4% Group 3	Comparisons: G 3 vs. G 1: p < 0.0001 G 2 vs. G 1: p < 0.0001 G 3 vs. G 2: p < 0.0027
RADICALS HD 0 vs. 6 mo. ADT [1067]	737 SRT 747 SRT+ADT	ISUP >7 (11%) ≥ pT3b (17%) R1 (62%) PSA: < 0.3 (61%) ≥ 0.5 (19%) R1 (62%) N1 (3%)	108	52.5Gy, 20fx PBRT (29%) 66Gy, 33fx PBRT (69%) LHRH analogue (83%)	10 yr. MFS: SRT: 79.2% SRT+ADT: 80.4% p = 0.71; HR: 0.89 CPFS: SRT: 68.3% SRT+ADT: 79.4% p = 0.071, HR:0.54	Max.GU-Tox G 3: SRT: 16% SRT+ADT: 13% p>0.05
RADICALS HD 6 versus 24 months ADT [1068]	761 6 mo. ADT 762 24 mo. ADT	ISUP > 7 (29%) ≥ pT3b (31%) Med. Pre SRT PSA: 0.23 R1 (63%) N1 (8%)	107	52.5Gy 20fx PBRT (19%) 66Gy, 33fx PBRT (79%) LHRH analogue (84%)	10 yr. MFS: SRT+6 mo.: 71.9% SRT+24 mo.: 78.1% p = 0.029, HR: 0.77	Max.GU-Tox G3: SRT+6 mo.: 14% SRT+24 mo.:20% p = 0.025

ADT = androgen deprivation therapy; CPFS = clinical progression free survival; DM = distant metastasis; DSM = disease specific mortality; PFS = progression free survival; FFP = Freedom From Progression; FU = follow-up; fx = fractions; LHRH = luteinising hormone-releasing hormone; MFS = metastasis-free survival; OS = overall survival; mo. = months; n = number of patients; yr. = years, PBRT = prostate bed radiotherapy; PFS = progression-free survival; PLNRT = pelvic lymph node radiotherapy; RT = radiotherapy; SRT = salvage ratiotherapy.

Table 6.4.6: Randomised trials investigating dose escalation for SRT without ADT and without PET-CT

Trial	n	PCa condition	Radiotherapy Dose	Follow-up (median)	Outcome	Results
SAKK 09/10 trial, 2021 [961]	350	pT2a-3b R0 – R1 pN0 or cN0 PSA post op undetectable (< 0.1ng/mL) or persistent (> 0.1ng/mL < 0.4ng/mL)	64Gy vs.70Gy No ADT allowed VMAT+ IGRT: 57% 3-D planning: 43%	6.2 yr.	Primary endpoint: FFBP	6 yr. FFBP: 62% vs. 61% OS: no difference Late side effects: GI grade 2: 7.3% vs. 20% GI grade 3: 4.2% vs. 2.3% p for ≥ grade 2/3: 0.009
Phase-III-Trial Qi X, *et al.*, 2024 [1082]	144 ART: 33% SRT: 67%	pT2-4 R0-R1 pN0 or cN0 Med. PSA pre-RT: 0.2ng/mL	66Gy vs.72Gy All patients VMAT+ IGRT No ADT allowed High risk (pT3-4, GS: 8-10, PSA >20ng/mL): whole pelvis RT: 126 (87.5%)	89.5 mo.	Primary endpoint: FFBP	7 yr. FFBP: 70.3% vs. 61.2% (p > 0.05) High risk (GS: 8–10): 66.5% vs. 30.2% p < 0.012 HR: 0.73 Multiple SR+: 82.5% vs. 57.5% p = 0.037 HR: 0.36 Late side effects: GI + GU grade 2 p > 0.05 No grade 3

ADT = androgen deprivation therapy; ART = adjuvant radiotherapy; FFBP = freedom from biochemical failure; GI = gastrointestinal; GU = genitourinary; Gy = Gray; IGRT = image guided radiotherapy; mo. = months; n = number of patients; PSA = prostate-specific antigen; RT = radiotherapy; SRT = salvage radiotherapy; VMAT = volumetric arc radiation therapy; vs. = versus; yr. = years.

6.4.5.a.2.b Salvage radiotherapy with or without ADT (pTx cN0/1) with PET/CT

In a prospective multicentre study of 323 patients with BCR, radiolabelled PSMA PET/CT changed the management intent in 62% of patients as compared to conventional staging. This was due to a significant reduction in the number of men in whom the site of disease recurrence was unknown (77% vs. 19%, p < 0.001) and a significant increase in the number of men with metastatic disease (11% vs. 57%) [1091]. A prospective study in a subgroup of 119 BCR patients with low PSA (< 0.5ng/mL) reported a change in the intended treatment in 30.2% of patients [1044]. However, no data exist on the impact on final outcome.

Another prospective study in 272 patients with early biochemical recurrent PCa after RP showed that ^{68}Ga-PSMA PET/CT may tailor further therapy decisions (e.g. local vs. systemic treatment) at low PSA values (0.2–1ng/mL) [1092].

A multicentre retrospective study evaluated patients who underwent SRT for BCR after RP, without any signs of distant metastatic disease on PET/CT. After case-control matching, an analysis was made of two cohorts (n = 108 patients each) with and without PSMA PET/CT prior to SRT. In the cohort without PSMA PET/CT, 23 patients (21%) had BCR at one year after SRT versus nine patients (8%) who underwent restaging with PSMA PET/CT prior to SRT (p = 0.007). Radiolabelled PSMA-PET/CT was found to be associated with an improved oncological outcome in patients with BCR after RP receiving SRT to the prostatic fossa [1093]. It is worth mentioning that, in this study, the median biologically effective radiation dose administered in the PSMA-cohort was significantly higher than in the historical cohort (70Gy vs. 66Gy, respectively, p < 0.001). The role of SRT to the prostatic fossa for patients with a negative PSMA-PET-CT for PSA progression after RP was investigated in a retrospective multicentre analysis of 1,222 patients [1094]. Exclusion of patients with pathological LN metastasis, PSA persistence after RP, LN metastasis, nodal irradiation or ADT led to a cohort of 341 patients with local positive PET or negative PET. The total dose to the fossa was significantly higher for patients with local PET positive findings (76.8% > 70 Gy vs. 77.5% < 70 Gy, p <0.001) and median pre SRT-PSA value was comparable (>0.2 and < 0.5 ng/mL) in both groups. With a median follow-up of 28 months the three-year BPFS was 71.6% in PET negative cases and 80.0% in locally PET positive cases (p > 0.05 in multivariate analysis). These data emphasise the importance of early SRT, even in PET-CT negative cases.

A single-centre open-label, phase II/III RCT (EMPIRE-1) evaluated the role of ^{18}F-fluciclovine-PET/CT compared with conventional imaging for SRT. Three hundred and sixty-five patients with detectable PSA after RP but negative results on conventional imaging were randomised to RT directed by conventional imaging alone or to conventional imaging plus PET/CT. Patients with M1 disease in the PET/CT group (n = 4) were excluded. Patients with cN1 were irradiated to the pelvic lymphatics but without a boost to the metastasis. Median follow-up was 3.5 years. In adjusted analyses, the study group was significantly associated with an improvement of the event-free survival (HR: 2.04, 95% CI: 1.06–3.93, p = 0.0327) [1095].

6.4.5.a.2.c Nodal-directed therapy for rcN1 (with PET/CT)

Radiolabelled PSMA PET/CT is increasingly used as a diagnostic tool to assess metastatic disease burden in patients with BCR following prior definitive therapy. A review including 30 studies and 4,476 patients showed overall estimates of positivity in a restaging setting of 38% in pelvic LNs and 13% in extrapelvic LN metastases [1051]. The percentage positivity of PSMA PET/CT was proven to increase with higher PSA values [1051]. Results of this review demonstrated a high sensitivity and specificity of ^{68}Ga-PSMA in advanced PCa with a per-lesion-analysed sensitivity and specificity of 75% and 99%, respectively.

A large retrospective international study included patients with LN-recurrent PCa (cN1 and M1a) and PSA progression following multimodality treatment (surgery and postoperative RT) [1096]. The aim of the study was to compare SOC with nodal metastasis-directed therapy (MDT). The nodal MDT-group showed significantly better CSS than the SOC control group (five-year survival 98.6% vs. 95.7%, p < 0.01, respectively) [1096].

Another retrospective study compared stereotactic body radiation therapy (SABR) with elective nodal irradiation (ENRT) in nodal oligo-recurrent PCa (n = 506 patients, 365 of which with N1 pelvic recurrence). With a median follow-up of 36 months, ENRT (n = 197) was associated with a significant reduction of nodal recurrences (p < 0.001), compared with SABR (n = 309) of 2% versus 18%, respectively. In a multivariable analysis, patients with one LN at recurrence had longer adjusted MFS after ENRT (HR: 0.50, 95% CI: 0.30–0.85, p = 0.009). The tendency to relapse was higher for pelvic than for extrapelvic nodes (p < 0.001) [1097]. For patients presenting with two or more pelvic or extra-pelvic LNs, adjusted MFS was not significantly different (HR: 0.92, 95% CI: 0.54–1.59, p = 0.8). In these situations, SABR should be used in highly selected patients in prospective cohorts or clinical trials only before any recommendations can be made.

A systematic review and pooled analysis concluded, although heterogeneity was high across all studies, the pooled rates of PSA- image- and systemic progressions were higher in LND compared with RT for BCR patients with PET-positive LNs [1098]. The pooled incidence from 19 publications for PSA-response were 51.1% (LND) and 74.3% (RT) and for PSA-progression 69.8% (LND) and 26.9% (RT).

The phase II randomised PEACE V-STORM trial compared salvage metastases directed therapy (MDT) and elective nodal RT for oligorecurrent nodal PCa in 196 patients [1099]. Patients in the MDT-group had salvage LND or SBRT (30 Gy in three fractions every other day), patients in the ENRT group received 45 Gy in 28 fractions with a simultaneous integrated boost to the PET-positive nodes (65 Gy), both groups had six months of ADT. Fifty-three patients (55%) in the MDT group and 58 patients (62%) in the ENRT group had one positive node, up to five positive nodes were eligible. PSA value at inclusion was 1 (0.53-2.32) in the MDT group and 0.85 (0.42-2.09) in the ENRT group, more than 80% had a PSMA-PET-CT. The primary endpoint was MFS. With a medium follow-up of 50 months the four-year MFS was 76% in the ENRT group compared with 63% in the MDT group (p = 0.063, HR: 0.62). The predominant recurrence pattern after MDT was locoregional (39%) compared with 18% in the ENRT group. However, in the STORM trial all 28 patients with pelvic nodal recurrence in the MDT arm received salvage SBRT, demonstrating that effective salvage treatments after SBRT are possible. The optimal duration of ADT is uncertain and durations > 6 months are likely to be more effective. These data have to be confirmed by a phase III trial.

6.4.5.a.3 Salvage lymph node dissection

Salvage lymph node dissection (SLND) is one form of metastases-directed therapy (MDT) which aims at surgically removing the site of nodal recurrence detected at PET imaging in patients who experience BCR following curative-intent therapies. Among the available phase II randomised trials assessing the role of MDT on oncologic control, only the STOMP study included a small number (n=5) of patients with oligo-recurrent PCa detected by choline PET/CT who were treated with SLND [1100], limiting its applicability to this setting. Therefore, current evidence is based on retrospective series.

An SR synthesised data from 27 series including patients restaged with choline or PSMA PET imaging and reported complete biochemical response after surgery in 13-79% of the cases with five-year BCR-free and

OS rates between 6%-31% and 84%, respectively [1101]. Prostate specific antigen value at salvage surgery and number and location of positive nodes at preoperative imaging represented preoperative predictors of biochemical response [1101]. The number of positive nodes at final pathology, pT stage and ISUP GG were postoperative predictors of biochemical control [1101]. An SR including 995 patients, with PET-detected nodal recurrence after RP, treated with SLND reported a pooled incidence of 51% in PSA response with PSA progression rates of 70% during follow-up [1098]. A large multi-centre retrospective study evaluated the long-term outcomes of 189 patients who underwent SLND for oligo-recurrent PCa and reported BCR-free survival of 11% at ten years. Patients with a PSA response after SLND and patients receiving ADT within six months from SNLD had a lower risk of death from PCa [1102]. Most of the patients (81%) received a choline PET and median PSA at SLND was 2.5 ng/mL. The addition of RT to the lymphatic template after salvage LN dissection may improve the BCR rate [1103]. High-level evidence for the oncological value of SLND (including adjuvant RT of the LNs) is still lacking [1101]. This limited evidence should be balanced against the risk of adverse postoperative events. Despite being considered safe, SLND is associated with a non-negligible risk of complications: up to 14% of patients in retrospective series experienced Clavien-Dindo grade 3b complications [1101]. This risk should be discussed during preoperative counselling, and the procedure is best performed in high-volume centres.

Studies including patients restaged with PSMA PET hybrid imaging focused on the role of radioguided surgery (RGS) have been performed. Data suggest that, in patients with node-recurrent PCa treated with SLND, RGS may offer important surgical guidance for surgeons, thus eventually improving oncologic outcomes [1104]. An SR of thirteen series showed that this technique achieved a decline in PSA levels > 90% in 22-100% of cases and BCR-free survival rates of 50-62% at a median follow-up of seventeen months [540]. Higher preoperative PSA, higher number of PSMA-avid lesions, multiple (pelvic plus retroperitoneal), and retroperitoneal localisation of lesions at preoperative imaging were independent predictors of BCR after PSMA-RGS [1105]. Moreover, patients achieving biochemical response of < 0.1 ng/ml were at lower risk of additional therapies at two-year follow-up [1105].

6.4.5.b Management of PSA failures after radiation therapy

Therapeutic options in these patients are ADT or salvage local procedures, as well as a 'wait and see' approach, based on EAU BCR risk categories at relapse. A SR and meta-analysis included studies comparing the efficacy and toxicity of salvage RP, salvage HIFU, salvage cryotherapy, SBRT, salvage LDR BT, and salvage HDR BT in the management of locally recurrent PCa after primary radical EBRT [1106]. The outcomes were BCR-free survival at two and five years. No significant differences with regards to recurrence-free survival (RFS) between these modalities was found. Five-year RFS ranged from 50% after cryotherapy to 60% after HDR BT and SBRT. The authors reported that severe GU toxicity exceeded 21% for whole-gland HIFU and RP, whereas it ranged from 4.2% to 8.1% with reirradiation. Differences in severe GI toxicity also appeared to favour re-irradiation, particularly HDR BT [1106]. Due to the methodological limitations of this review (the majority of the studies included were uncontrolled single-arm case series and there was considerable heterogeneity in the definitions of core outcomes) the available evidence for these treatment options is of low quality and strong recommendations regarding the choice of any of these techniques cannot be made. The following is an overview of the most important findings for each of these techniques.

6.4.5.b.1 Salvage radical prostatectomy

Salvage RP may be a curative-intent option for selected patients with biopsy-confirmed local recurrence after RT without evidence of nodal or distance metastases at restaging (namely, PSMA PET). This procedure is associated with a higher likelihood of AEs compared to primary surgery because of the risk of fibrosis and poor wound healing due to radiation [1107].

6.4.5.b.1.a Oncological outcomes

An SR evaluated 3,836 patients in 55 studies with median follow-up ranging from 4.6–94 months and showed that SRP provided five-year BCR occurrence 48-59%, cancer-specific survival 13.4-98%, and overall survival 62-100% [1108]. These figures are similar to those reported by Chade *et al.* in 2011, with five-year and 10-year BCR-free survival estimates ranging from 47–82% and from 28–53%, respectively. The 10-year CSS and OS rates ranged from 70–83% and from 54–89%, respectively. Importantly, most of these findings were based on patient cohorts restaged using conventional imaging at the time of BCR. It may be hypothesised that the adoption of more accurate imaging modalities, such as PSMA/PET, could preoperatively identify patients with nodal or distant metastases who would not be eligible for SRP, thereby improving patient selection and potentially enhancing oncological outcomes. A study evaluating 568 patients with rising PSA levels after primary radiotherapy who underwent PSMA PET/CT found that isolated local recurrence was detected in only 32% of patients meeting the Phoenix criteria for BCR after RT, while distant metastases were present in 49% of these cases [1109]. The pre-SRP PSA value and initial prostate biopsy ISUP grade group were the strongest predictors of the presence of organ-confined disease, progression, and CSS [1110]. In a multicentre analysis including 414

patients, five-year BCR-free survival, CSS and OS were 56.7%, 97.7% and 92.1%, respectively [1111]. Pathological T stage ≥ T3b (OR: 2.348) and GS (up to OR: 7.183 for ISUP GG 4-5) were independent predictors for BCR. Appropriate risk-stratification according to EAU Guidelines Biochemical Recurrence criteria may better select for SRP, with higher metastasis-free (90% vs 76%, p < 0.01) and overall survival (89% vs. 84%, p = 0.01) for low versus high EAU risk [1112, 1113].

Lymphadenectomy was performed in most cases (79%), with 20.5% of patients staged N+ at final pathology [1108]. Detailed analysis of a multi-institutional series of 853 SRP patients reported that 87% underwent lymphadenectomy, 21% were pN1 and these patients suffered worse overall and cancer-specific survival [1114]. As in primary surgery, patients with persistent PSA after SRP (42%) had worse BCR-free (6.6 vs. 59%), metastasis-free (71 vs. 88%) and overall survival (77 vs. 94%) after median follow-up of 84 months according to a retrospective, multi-institutional series of 580 patients [1115]. Persistent PSA after SRP was shown to be an independent predictor for BCR and death.

6.4.5.b.1.b Morbidity

Most reported cases have been open (60%) and robotic-assisted (38%), resulting in an overall complication rate of 34%, with major (Clavien grade ≥ 3) complications occurring across a range of 0- 64% [1108]. Compared to primary open RP, SRP is associated with a higher risk of later anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs. 3.5%), urinary fistula (4.1% vs. 0.06%), abscess (3.2% vs. 0.7%) and rectal injury (9.2 vs. 0.6%) [1116]. These complications appear to be less common with robotic compared to open surgery [1107, 1110, 1117]. An SR including 1,630 patients treated with SRP from 33 series reported intraoperative complication rates of up to 9%, while postoperative complication rates ranged from 0% to 90% [1118].

Functional outcomes are also worse compared to primary surgery, considering urinary incontinence (47.9%, range 21%- 90%) and ED in nearly all patients [1108, 1110, 1117].

6.4.5.b.1.c Summary of salvage radical prostatectomy

In general, SRP should be considered only in selected patients with biopsy-proven local recurrence disease after RP with a PSMA PET negative for nodal or distant metastases, low comorbidity burden, a life expectancy of at least ten years, a pre-SRP PSA < 10 ng/mL, initial biopsy ISUP grade group ≤ 2/3, and those whose initial clinical staging was T1 or T2 [1110].

6.4.5.b.2 Salvage cryoablation of the prostate

6.4.5.b.2.a Oncological outcomes and morbidity

Salvage cryoablation of the prostate (SCAP) has been proposed as an alternative to salvage RP, because it has a potentially lower risk of morbidity and equal efficacy.

In an SR, a total of 32 studies assessed SCAP, recruiting a total of 5,513 patients. The overwhelming majority of patients (93%) received whole-gland SCAP. The adjusted pooled analysis for two-year BCR-free survival for SCAP was 67.49% (95% CI: 61.68–72.81%), and for five-year BCR-free survival was 50.25% (95% CI: 44.10–56.40%). However, the certainty of the evidence was low. Table 6.4.7 summarises the results of a selection of the largest series on SCAP to date in relation to oncological outcomes (BCR only) [1106]. An SR and meta-analysis including 36 studies confirmed an RFS of 67.6%, 59.5% and 47.3% at two, three and five years, respectively [1119]. The authors describe a lower recurrence rate when PSA was < 5ng/mL, the time from primary radiation was > 70 months, when whole gland cryotherapy was performed, and adjuvant ADT was used. Overall, the morbidity was acceptable with 8.5% urinary incontinence, 3% sloughing/stenosis and 1% recto-vesical fistula.

Table 6.4.7: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients

Study	n	Median FU (mo)	Time point of outcome measurement (yr)	BCR-free probability	Definition of failure
Ginsburg, *et al.* 2017 [1120]	898	19.0	5 yr.	71.3%	Phoenix criteria
Spiess, *et al.* 2010 [1121]	450	40.8	3.4 yr.	39.6%	PSA > 0.5 ng/mL
Campbell *et al.* 2023 [1122]	419	72	5 yr.	74.6% Cyo as primary 78.5% RT as primary	Phoenix criteria
Li, *et al.* 2015 [1123]	486	18.2	5 yr.	63.8%	Phoenix criteria

Kovac, *et al.* 2016 [1124]	486	18.2	5 yr.	75.5% (nadir PSA < 0.4ng/mL); 22.1% (nadir PSA ≥ 0.4ng/mL)	Phoenix criteria
Ahmad, *et al.* 2013 [1125]	283	23.9	3 yr.	67.0% (nadir PSA ≤ 1ng/mL); 14.0% (nadir PSA > 1ng/mL)	Phoenix criteria
Pisters, *et al.* 2008 [1126]	279	21.6	5 yr.	58.9% (ASTRO) 54.5% (Phoenix)	ASTRO and Phoenix criteria

ASTRO = American Society for Therapeutic Radiology and Oncology; BCR = biochemical recurrence; FU = follow-up; mo. = months; n = number of patients; PSA = prostate-specific antigen; Cyo = cryoablation; RT = radiotherapy; yr. = years.

6.4.5.b.3 ***Salvage re-irradiation***

6.4.5.b.3.a Salvage brachytherapy for radiotherapy failure

Carefully selected patients with a good PS, primary localised PCa, good urinary function and histologically proven local recurrence are candidates for salvage BT using either HDR or LDR.

In an SR, a total of 16 studies (four prospective) and 32 studies (two prospective) assessed salvage HDR and LDR BT, respectively, with the majority (> 85%) receiving whole-gland BT rather than focal treatment [1106]. The adjusted pooled analysis for two-year BCR-free survival for HDR was 77% (95% CI: 70–83%) and 81% for LDR (95% CI:74–86%). The five-year BCR-free survival for HDR was 60% (95% CI: 52–67%) and for LDR was 56% (95% CI: 48–63%). As noted above, BT techniques are associated with lower rates of severe GU toxicity when compared to RP or HIFU, at 8% for HDR (95% CI: 5.1–11%) and 8.1% for LDR (95% CI: 4.3–13%). Rates of severe GI toxicity are reported to be very low at 0% for HDR (95% CI: 0–0.2%) and 1.5% for LDR (95% CI: 0.2–3.4%). High-dose-rate or LDR BT are effective treatment options with an acceptable toxicity profile. However, the published series are small and likely under-report toxicity. Consequently, this treatment should be offered in experienced centres, ideally within randomised clinical trials or prospective registry studies (see Table 6.4.8).

Table 6.4.8: Treatment-related toxicity and BCR-free probability in selected salvage brachytherapy studies including at least 100 patients.

Study	Study design	n and BT type	Median FU (mo)	Treatment toxicity	BCR-free probability
Lopez, *et al.* 2019 [1127]	multi-centre retrospective	75 HDR 44 LDR	52	23.5% late G 3+ GU	5 yr. 71% (95% CI: 65.9-75.9%)
Crook, *et al.* 2019 [1128]	multi-centre prospective	100 LDR	54	14% late G 3 combined GI/GU	n.r.
Smith, *et al.* 2020 [1129]	single-centre retrospective	108 LDR	76	15.7%/2.8% late G 3 GU/GI	5 yr. 63.1% 10 yr. 52%
Lyczek, *et al.* 2009 [1130]	single-centre retrospective	115 HDR	n.r.	12.2%/0.9% late G 3+ GU/GI	60% at 40 mo.

BCR = biochemical recurrence; BT = brachytherapy; CI = confidence interval; FU = follow-up; G = grade; GI = gastrointestinal; GU = genitourinary; HDR = high dose rate; LDR = low dose rate; mo. = months; n = number of patients; n.r. = not reported; yr. = years.

6.4.5.b.3.b Salvage stereotactic ablative body radiotherapy for radiotherapy failure

6.4.5.b.3.b.1 Oncological outcomes and morbidity

Stereotactic ablative body radiotherapy (CyberKnife® or linac-based treatment) is a potentially viable new option to treat local recurrence after RT. Carefully selected patients with good IPSS score, without obstruction, good PS and histologically proven localised local recurrence are potential candidates for SABR. In a meta-analysis and SR five mostly retrospective studies including 206 patients were treated with CyberKnife® or linac-based treatment showing two-year RFS estimates (61.6%, 95% CI: 52.6–69.9%) [1106]. In a retrospective multicentre study (n = 100) the median pre-salvage PSA was 4.3ng/mL with 34% of patients having received ADT for twelve months (median). All recurrences were biopsy proven. Patients were treated with the CyberKnife® with a single dose of 6Gy in six daily fractions (total dose 36Gy). With a median follow-up of 30 months the estimated three-year second BCR-free survival was 55% [1131].

In a smaller retrospective series including 50 men with histologically proven local recurrence with a median pre-salvage PSA of 3.9ng/mL only 15% had received additional ADT. The estimated five-year second BCR-free survival was 60% (median follow-up of 44 months) which is an outcome comparable to series treating patients with RP, HIFU or BT [1132]. Table 6.4.9 summarises the results of the two larger SABR series addressing oncological outcomes and morbidity.

Table 6.4.9: Treatment-related toxicity and BCR-free survival in selected SABR studies

Study	Study design	n and RT type	Median FU (mo.)	Fractionation (SD/TD)	ADT	Treatment toxicity	BCR-free survival
Bergamin, *et al.* 2020 [1133]	single-centre prospective	25 LINAC based	25	SD 6-6.2 TD 36-38Gy	0/25	2 yr. late G1 GI 8% G2 GU 4%	2 yr. 80%
Fuller, *et al.* 2020 [1132]	single-centre retrospective	50 Cyber Knife	44	SD 6.8Gy TD 34Gy	7/50	5 yr: 8% late G3+ GU	5 yr. 60%
Pasquier, *et al.* 2020 [1131]	multicentre retrospective	100 Cyber Knife	30	SD 6Gy TD 36Gy	34/100 median 12 mo.	3 yr. grade 2+ GU 20.8% GI 1%	3 yr. 55%

ADT = androgen deprivation therapy; BCR = biochemical recurrence; FU = follow-up; G = grade; GI = gastrointestinal; GU = genitourinary; mo. = months; n = number of patients; RT type = type of radiotherapy; SD = single dose; TD = total dose; yr. = years.

6.4.5.b.3.b.2 Morbidity

In a retrospective single-centre study with 50 consecutive patients, chronic significant toxicity was only seen for the GU domain with five-year grade 2+ and grade 3+ GU rates of 17% and 8%, respectively. No GI toxicity > grade 1 was seen. Of note, of the fifteen patients who were sexually potent presalvage SBRT, twelve subsequently lost potency [1132]. In a retrospective French (GETUG) multicentre series (n = 100) the three-year late grade 2+ GU and GI toxicity was 20.8% (95% CI: 13–29%) and 1% (95% CI: 0.1–5.1%), respectively [1131]. A SR and meta-analysis demonstrated salvage SABR resulted in comparable rates of G3+ GU toxicity when compared to salvage cryotherapy and brachytherapy, but substantially lower rates than salvage HIFU [1134].

6.4.5.b.3.b.3 Summary of salvage stereotactic ablative body radiotherapy

Despite the encouraging results so far, the number of patients treated with SABR is relatively limited. In view of the rates of higher-grade 2+ GU side effects, SABR should only be offered to selected patients, in experienced centres as part of a clinical trial or well-designed prospective study.

6.4.5.b.4 Salvage high-intensity focused ultrasound

6.4.5.b.4.a Oncological outcomes

Salvage HIFU has emerged as an alternative thermal ablation option for radiation-recurrent PCa. Being relatively newer than SCAP the data for salvage HIFU are even more limited. A SR and meta-analysis included 20 studies (n = 1,783) assessing salvage HIFU [1106], which was also confirmed by another SR and meta-analysis [1134]. The overwhelming majority of patients (86%) received whole-gland salvage HIFU. The adjusted pooled analysis for two-year BCR-free survival for salvage HIFU was 54.14% (95% CI: 47.77–60.38%) and for five-year BCR-free survival 52.72% (95% CI: 42.66–62.56%). However, the certainty of the evidence was low. Table 6.4.10 summarises the results of a selection of the largest series on salvage HIFU to date in relation to oncological outcomes (BCR only).

Table 6.4.10: Oncological results of selected salvage cryoablation of the prostate case series, including at least 250 patients

Study	n	Median FU (mo.)	Time point of outcome measurement	BCR-free probability	Definition of failure
Crouzet, *et al.* 2017 [1135]	418	39.6	5 yr.	49.0%	Phoenix criteria
Murat, *et al.* 2009 [1136]	167	Mean 18.1	3 yr.	25.0% (high-risk) 53.0% (low-risk)*	Phoenix criteria or positive biopsy or initiation of post-HIFU salvage therapy

Kanthabalan, *et al.* 2017 [1137]	150	35.0	3 yr.	48.0%	Phoenix criteria
Jones, *et al.* 2018 [1138]	100	12.0	1 yr.	50.0%	Nadir PSA > 0.5 ng/mL or positive biopsy

***Results stratified by pre-EBRT D'Amico risk groups.*
BCR = biochemical recurrence; FU = follow-up; HIFU = high-intensity focused ultrasound; mo. = months; n = number of patients; yr. = years.

6.4.5.b.4.b Morbidity

The main adverse effects and complications relating to salvage HIFU include urinary incontinence, urinary retention due to bladder outflow obstruction, rectourethral fistula and ED. The SR and meta-analysis showed an adjusted pooled analysis for severe GU toxicity for salvage HIFU of 22.66% (95% CI: 16.98–28.85%) [1106]. The certainty of the evidence was low. Table 6.4.11 summarises the results of a selection of the largest series on salvage HIFU to date in relation to GU outcomes.

.Table 6.4.11: Peri-operative morbidity, erectile function and urinary incontinence in selected salvage HIFU case series, including at least 100 patients

Study	n	Time point of outcome measurement (yr.)	Incontinence* (%)	Obstruction/ retention (%)	Rectourethral fistula (%)	ED (%)
Crouzet, *et al.* 2017 [1135]	418	Median 39.6	42.3	18.0	2.3	n.r.
Murat, *et al.* 2009 [1136]	167	Median 18.1	49.5	7.8	3.0	n.r.
Kanthabalan, *et al.* 2017 [1137]	150	24	12.5	8.0	2.0	41.7
Jones, *et al.* 2018 [1138]	100	12	42.0	49.0	5.0	74.0

**Incontinence was heterogeneously defined; figures represent use of at least one pad.*
ED = erectile dysfunction; n.r. = not reported; n = number of patients; yr. = years.

6.4.5.b.4.c Summary of salvage high-intensity focused ultrasound

There is a lack of high-certainty data, which prohibits any recommendations regarding the indications for salvage HIFU in routine clinical practice. There is also a risk of significant morbidity associated with its use in the salvage setting. Consequently, salvage HIFU should only be performed in selected patients in experienced centres as part of a clinical trial or well-designed prospective cohort study.

6.4.6 Hormonal therapy for relapsing patients

The aim of hormonal therapy (ADT) in relapsing patients is to improve OS, delay the onset of distant metastases, and maintain QoL. Biochemical response alone to ADT holds no clinical benefit for a patient. An SR including studies published from 2000 onwards [1139], found conflicting results on the clinical effectiveness of ADT after previous curative therapy. Some studies reported a favourable effect of ADT, including the only RCT addressing the research question of this review (86% vs. 79% advantage in OS in the early ADT group) [1140]. Other studies did not find any differences between early versus delayed, or no, ADT. One study found an unfavourable effect of ADT [1141]. Variability appears to be driven by heterogeneous tumour biology with only a minority progressing to metastases or PCa-related death. For older patients and those with comorbidities, the side effects of ADT may even decrease life expectancy. Cardiovascular risk factors in particular must be considered [1142, 1143]. The benefit of early ADT seems most evident in high-risk patients, mainly defined by a high ISUP GG and a short PSA-DT (most often less than six months) and a long-life expectancy [1144].

This is supported in a three-arm randomised phase III trial (EMBARK) which evaluated response in patients with prostate cancer who had high-risk biochemical recurrence defined as a PSA-DT of ≤ 9 months and a PSA level of ≥ 2ng/mL above the nadir after radiation therapy or ≥ 1ng/mL after radical prostatectomy with or without postoperative radiation therapy [1145]. Patients were randomly assigned 1:1:1 to receive enzalutamide daily plus leuprolide every 12 weeks (combination group), placebo plus leuprolide (leuprolide-alone group), or enzalutamide monotherapy (monotherapy group). The primary end point was MFS, as assessed by blinded

independent central review, in the combination group as compared with the leuprolide-alone group. A key secondary end point was MFS in the monotherapy group as compared with the leuprolide-alone group. Other secondary end points were patient-reported outcomes and safety. A total of 1,068 patients were randomised. After a median follow-up of 60.7 months, the five-year MFS was 87.3% (95% CI, 83.0-90.6) in the combination group, 71.4% (95% CI, 65.7-76.3) in the leuprolide-alone group, and 80.0% (95% CI, 75.0-84.1) in the monotherapy group. The combination of enzalutamide plus leuprolide was superior to leuprolide alone with regards to the MFS (HR 0.42; 95% CI, 0.30-0.61; p < 0.001). Enzalutamide monotherapy also showed a superior MFS compared to leuprolide alone (HR 0.63; 95% CI, 0.46-0.87; p = 0.005). These results led to the FDA approval for enzalutamide alone or in combination with ADT for patients with high-risk biochemical recurrence in November 2023 [1146], followed by EMA approval in April 2024 [1147].

The 2025 update of this study present eight-year OS. In the combination group the OS was 78.9% (95% CI 73.9-83.1) and 69.5% (95% CI 64.0-74.3) in the leuprolide-alone group; the HR for death was 0.60 (95% CI 0.44-0.80; p < 0.001). The eight-year OS with monotherapy was 73.1% (95% CI 67.6-77.9), which did not differ significantly from that with leuprolide alone (HR 0.83; 95% CI 0.63-1.10; p = 0.19). This led to the conclusion that OS was significantly longer with the combination of enzalutamide and leuprolide than with leuprolide alone among patients with PCa with high-risk BCR. Enzalutamide monotherapy was not superior to leuprolide alone in the analysis of OS. These findings support the use of enzalutamide with ADT in high-risk BCR patients with a PSA-DT ≤ 9 months and a PSA above predefined thresholds following local therapy [1148].

A Scandinavian phase-III trial (SPCG-14) [1149] evaluated the effect of docetaxel added to bicalutamide in hormone-naive nonmetastatic PCa with a rising PSA after radical treatment (prostatectomy or radiotherapy, n = 315) or not suitable for curative treatment (n = 3). Between 2009 and 2018, 348 patients were randomised, and median follow up was 4.9 years. As no MFS data are available and the primary endpoint was PFS only, no recommendation for the addition of docetaxel in this setting of PSA recurrence can be made at this time.

6.4.7 Recommendations for second-line therapy after treatment with curative intent

Recommendations for local salvage treatment	Strength rating
Biochemical recurrence (BCR) after radical prostatectomy	
Offer early salvage intensity-modulated radiotherapy/volumetric arc radiation therapy plus image-guided radiotherapy to men with two consecutive prostate-specific antigen (PSA) rises.	Strong
Offer monitoring, including PSA, to EAU low-risk BCR patients.	Weak
Do not wait for a PSA threshold before starting treatment. Once the decision for salvage radiotherapy (SRT) has been made, SRT (at least 64 Gy) should be given as soon as possible.	Strong
Offer hormonal therapy in addition to SRT to men with BCR.	Weak
Follow-up after radical prostatectomy or radiotherapy	
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and serum PSA measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong
BCR after radiotherapy	
Offer monitoring, including PSA, to EAU Low-Risk BCR patients.	Weak
Offer highly selected patients with biopsy-proven local recurrence salvage radical prostatectomy, brachytherapy, stereotactic body radiotherapy in experienced centres.	Strong
Offer highly selected patients with biopsy-proven local recurrence high-intensity focused ultrasound, or cryosurgical ablation within a clinical trial setting or well-designed prospective cohort study	Weak
Systemic salvage treatment	
Do not offer androgen deprivation therapy (ADT) to M0 patients with a PSA-doubling time > 12 months.	Strong
Offer enzalutamide with ADT to EMBARK-like patients (M0 patients on conventional imaging and PSA doubling time of ≤ 9 months).	Strong

6.5 Systemic treatments for prostate cancer

6.5.1 Hormonal therapy

Androgen deprivation can be achieved by suppressing the secretion of testicular androgens in various ways.

6.5.1.a Castration level

The castration level of testosterone is < 50ng/dL (1.7 nmol/L), defined more than 40 years ago when testosterone testing was less sensitive. Current methods have shown that the mean value after surgical castration is 15ng/dL [1035]. Therefore, a preferred target level should be defined as < 20ng/dL (< 0.7 nmol/L). This definition is important because better results are repeatedly observed in ADT monotherapy cohorts with lower testosterone levels compared to 50ng/dL [1036-1038]. However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is still the historical < 50ng/dL (1.7 nmol/L).

6.5.1.b Bilateral orchiectomy

Bilateral orchiectomy or subcapsular pulpectomy is still considered the primary treatment modality for ADT. It is a simple, cheap and low-complication procedure. It is easily performed under local anaesthesia and is the quickest way to achieve a castration level that is usually reached within less than twelve hours. It is irreversible and therefore does not allow for intermittent treatment [1039].

6.5.1.c Luteinising-hormone-releasing hormone agonists

Long-acting LHRH agonists are currently the main stay of ADT. These synthetic analogues of LHRH are administered as depot injections on a monthly, three-monthly, six-monthly or yearly schedule. The first injection induces a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH), leading to the 'testosterone surge' or 'flare-up' phenomenon, which starts two to three days after administration and lasts for approximately one week. This transient hormonal rise has historically been associated with potentially detrimental clinical effects (the clinical flare), such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression and cardiovascular death due to hypercoagulation status [1150]. Patients at risk are typically those with high-volume symptomatic bone metastases. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare but does not completely remove the risk. Anti-androgen therapy is usually continued for four weeks but neither the timing nor the duration of anti-androgen therapy are based on strong evidence. Moreover, the long-term benefit of flare prevention remains unclear [1151]. Notably, more recent analyses question the clinical relevance of this testosterone flare in most patients, suggesting limited evidence for significant PSA increases, disease progression, or complications directly attributable to the flare. The need for anti-androgens at initiation may therefore be limited to selected high-risk cases [1151, 1152].

Chronic exposure to LHRH agonists results in the downregulation of LHRH receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within two to four weeks [1153]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [1154]. No survival difference between LHRH agonists and orchiectomy has been reported, due to the lack of high-quality comparative trials [1155]. The various products have practical differences that must be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drug is given by subcutaneous or intramuscular injection.

6.5.1.d Luteinising-hormone-releasing hormone antagonists

Luteinising-hormone-releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds as injections is the lack of a long-acting depot formulation with, so far, only monthly formulations being available. Degarelix is a LHRH antagonist. The standard dosage is 240 mg in the first month, followed by monthly injections of 80 mg. Most patients achieve a castrate level at day three [1153]. A phase III RCT compared degarelix to monthly leuprorelin following up patients for twelve months, suggesting a better PSA PFS for degarelix 240/80 mg compared to monthly leuprorelin [1156]. An SR did not show a major difference between agonists and degarelix and highlighted the paucity of on-treatment data beyond twelve months, as well as the lack of survival data [1157]. Its definitive superiority over the LHRH analogues remains to be proven. Short-term follow-up data from a meta-analysis indicate that the use of LHRH antagonist is associated with significantly lower overall mortality and cardiovascular events as compared with agonists. On the other hand, other adverse effects, such as decreased libido, hot flushes, ED, weight gain and injection site reactions, are seen less often with the agonists [1158, 1159].

Relugolix is an oral LHRH antagonist. It was compared to the LHRH agonist leuprolide in a randomised phase III trial [1160]. The primary endpoint was sustained testosterone suppression to castrate levels through 48 weeks. There was a significant difference of 7.9 percentage points (95% CI: 4.1–11.8) showing noninferiority and superiority of relugolix. The incidence of major adverse cardiovascular events was significantly lower with relugolix (prespecified safety analysis). Relugolix has been approved by the FDA [1161] and EMA [1162] for hormone sensitive PCa.

6.5.1.e Anti-androgens

These oral compounds are classified according to their chemical structure as:

- steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate; and
- non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This leads to an unchanged or slightly elevated testosterone level. Conversely, steroidal anti-androgens have progestational properties leading to central inhibition by crossing the blood-brain barrier.

6.5.1.e.1 Steroidal anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side effects are secondary to castration (gynaecomastia is quite rare) whilst the non-pharmacological side effects are cardiovascular toxicity (4–40% for CPA) and hepatotoxicity.

Cyproterone acetate was the first licensed anti-androgen but the least studied. Its most effective dose as monotherapy is still unknown. It appears to be associated with a poorer OS when compared with LHRH analogues and there is no benefit when compared with flutamide [1163, 1164].

6.5.1.e.2 Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy with e.g. nilutamide, flutamide or bicalutamide does not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [1165]. Non-androgen-related pharmacological side effects differ between agents. Bicalutamide shows a more favourable safety and tolerability profile than flutamide and nilutamide [1166]. The dosage licensed for use in combination with LHRH blockade is 50mg/day, and 150mg/day for monotherapy. The androgen pharmacological side effects are mainly gynaecomastia (70%) and breast pain (68%). However, non-steroidal anti-androgen monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [1165, 1167]. All three agents share the potential for liver toxicity (occasionally fatal), requiring regular monitoring of patients' liver enzymes.

6.5.1.e.3 New androgen receptor pathway inhibitors (ARPIs)

Once on ADT, the development of castration-resistance (CRPC) is only a matter of time. It is considered to be mediated through two main overlapping mechanisms: androgen-receptor (AR)-independent and AR-dependent mechanisms. In CRPC, the intracellular androgen level is increased compared to androgen-sensitive cells and an overexpression of the AR has been observed, suggesting an adaptive mechanism [1168]. This has led to the development of several compounds targeting the androgen axis. Table 6.5.1 summarises the status of the various ARPIs [1169-1174]. For the updated approval status, see the EMA and FDA websites [1146, 1175-1178].

Table 6.5.1: Status of the different ARPIs

	High-risk localised & locally advanced**	High-risk BCR	mHSPC	nmCRPC	mCRPC
Abiraterone	X*		X		X
Enzalutamide		X	X	X	X
Apalutamide			X	X	
Darolutamide			X	X	

** Unlicenced indication*

*** STAMPEDE definition*

6.5.1.e.3.a Abiraterone acetate

Abiraterone acetate is a CYP17 inhibitor (a combination of 17α-hydrolase and 17,20-lyase inhibition). By blocking CYP17, abiraterone acetate significantly decreases the intracellular testosterone level by suppressing

its synthesis at the adrenal level and inside the cancer cells (intracrine mechanism). This compound must be used together with prednisone/prednisolone to prevent drug-induced hyperaldosteronism [1175, 1177].

6.5.1.e.3.b Apalutamide, darolutamide, enzalutamide and rezvilutamide

These agents are novel non-steroidal antiandrogens with a higher affinity for the AR receptor than traditional non-steroidal antiandrogens. In addition, while previous non-steroidal antiandrogens still allow transfer of ARs to the nucleus and would act as partial agonists, all four agents also block AR transfer and therefore suppress any possible agonist-like activity [1169, 1170, 1178, 1179]. Darolutamide has structurally unique properties. In particular, in preclinical studies darolutamide was shown not to cross the blood-brain barrier [1180, 1181].

*6.5.2 **Cytotoxic drug treatment***

6.5.2.a Taxanes

Paclitaxel derivatives promote the assembly of microtubules and inhibit the subsequent depolymerisation, impairing the tubulin dynamics that foster the mitotic spindle assembly during interphase in mitosis [1182]. Docetaxel binds ß-tubulin dimers in a 1:1 stoichiometric ratio, exhibiting a stronger dynamic instability using its inhibitory effect in tubulin depolymerisation [1183]. It also activates NF-kB causing apoptosis via a mitochondria-dependent pathway [1184]. Docetaxel shows significant activity against prostate tumours. Cabazitaxel also works by binding to the microtubules. This prevents cellular mitosis and stabilises the tumour cells. As a result, the cells do not divide. In addition, it inhibits androgen receptors by binding to the microtubules and microtubule-associated motor protein dynein. As a consequence, androgen receptor nuclear translocation is prevented [1182]. Common side effects include peripheral neuropathy, myalgias, neutropenia and arthralgia.

*6.5.3 **Nonhormonal noncytotoxic drug treatments***

6.5.3.a Poly (ADP-ribose) polymerase inhibitors (PARPi)

Poly (ADP-ribose) polymerase inhibitors (PARPi) block the enzyme poly ADP-ribose polymerase (PARP) and were developed aiming to selectively target cancer cells harbouring *BRCA* mutations and other mutations inducing homologous recombination deficiency and a high level of replication pressure with a sensitivity to PARPi treatment. Due to the oncogenic loss of some DNA repair effectors and incomplete DNA repair repertoire, some cancer cells are addicted to certain DNA repair pathways such as Poly (ADP-ribose) polymerase (PARP)-related single-strand break repair pathway. The interaction between *BRCA* and PARP is a form of synthetic lethal effect, which means the simultaneously functional loss of two genes leads to cell death, while a defect in any single gene only has a limited effect on cell viability [1185]. *BRCA* mutations predispose patients to the development of PCa whilst also making tumours more responsive to PARPi. Therefore, *BRCA* status should be assessed in patients with metastatic PCa for optimal treatment selection.

6.5.3.b *Immune checkpoint inhibitors*

Checkpoint inhibitors target the molecules CTLA4, programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1). For advanced PCa patients who are microsatellite instability-high/deficient mismatch repair (MSI-H/*dMMR*), the PD-1 inhibitor pembrolizumab has been approved by the FDA but not by the EMA. The label is tumour agnostic [1186, 1187].

6.5.3.c Radiopharmaceutical therapy

Radiopharmaceutical therapy (RPT) is based on the delivery of radioactive isotopes to tumour-associated targets. The mechanism of action for RPT is radiation-induced killing of cells. Radionuclides with different emission properties are used to deliver radiation. The most commonly used radionuclides are represented by β-particles (e.g. ^{177}Lu) or α-particles (e.g. ^{223}Ra, ^{225}Ac). ^{223}Ra based on its biochemical similarity to Calcium, is integrated in bones with increased osteoblastic activity, thus targeting skeletal PCa metastases. ^{177}Lu is increasingly used because of its optimal imaging range (100–200keV), favourable half time (6.6 days), and appropriate β-particle energy for therapy. The short path of the β-particles (0.05–0.08 mm) results in minimal toxic effects in adjacent healthy tissue. These properties enable such radionuclides to be used as theranostics (i.e. the same radionuclide may be used for both diagnostic and therapeutic purposes). However, an essential requirement prior to any RPT is to assess the targeting of the agent, mainly using PET techniques which show the tumour expression and the extent of cancer [1188]. The FDA has approved ^{177}Lu for the treatment of adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy [1189, 1190].

6.5.3.d AKT inhibitors

AKT inhibitors are orally administered ATP-competitive molecules that target the three AKT isoforms. AKT propagates signals from the PI3K/AKT/mTOR pathway which is central for promoting cell survival, proliferation, metabolism, and growth. AKT inhibitors interrupt key growth and survival signals in cancer cells by locking AKT into an inactive state and preventing downstream phosphorylation.

6.6 Management of metastatic prostate cancer

6.6.1 Introduction

Most prospective data available rely on the definition of M1 disease based on CT scan or MRI and bone scintigraphy. Modern, more accurate imaging is increasingly being applied in clinical practice; however, its influence on treatment and patient outcomes has not yet been validated in prospective RCTs.

6.6.2 Molecular testing

Different techniques may be applied for molecular testing including immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), and next generation sequencing (NGS) of RNA or DNA. Treatment should be based on predictive [1191] and not prognostic genetic aberrations. Patients potentially eligible for treatment intensification should be offered somatic DNA sequencing using panel-based assays [1191]. Assay failure rates are lower on more recently collected primary tumour tissue or on tissue from metastases. Although useful information has been extracted from tissue up to five to ten years old [1192]. Genetic testing on circulating tumour DNA (ctDNA) is an alternative option and has been used in some trials. The FoundationOne® Liquid CDx, has been FDA approved [1220]. Certified (accredited) institutions should be used for NGS multiplication procedure (minimum depth of coverage of 200 X). A critical asset is the decision support helping to rate the mutations according to their clinical relevance [1193, 1194]. Defective *MMR* assessment can be performed by IHC for *MMR* proteins (*MSH2, MSH6, MLH1* and *PMS2*) and/or by next generation sequencing (NGS) assays [1195]. For patients with metastatic disease and assay failure germline testing is recommended to identify *BRCA 1/2* alterations. Germline molecular testing is discussed in Section 5.1.6 and recommendations for germline testing are provided in Section 5.2.8. Level 1 evidence for the use of PARP inhibitors has been reported [341, 1196-1207]. Microsatellite instability (MSI) high (or *MMR* deficiency) is rare in PCa, but for those patients, pembrolizumab has been approved by the FDA and could be a valuable additional treatment option [1187, 1208].

6.6.3 Prognostic and predictive factors

Median survival of patients with newly diagnosed metastases (synchronous mHSPC) is approximately 50 months with ADT alone, however, it is highly variable since the M1 population is heterogeneous [1209]. Several prognostic factors for survival have been suggested, including the number and location of bone metastases, presence of visceral metastases, ISUP GG, performance status and initial PSA and alkaline phosphatase level, but only few have been validated [1210-1213].

'Volume' of disease as a potential predictor was introduced by CHAARTED (Chemohormonal Therapy versus Androgen Ablation Randomised Trial for Extensive Disease in Prostate Cancer) [1213-1215] (Table 6.6.1) and subsequently, in STAMPEDE, was shown to be predictive in an adequately powered subgroup analysis for benefit of addition of prostate RT to ADT in the subgroup of patients with low volume/burden disease [1216] (Table 6.6.1).

'Metachronous' metastatic disease (after radical local treatment of the primary tumour) vs. synchronous (or *de novo*) metastatic disease has also been shown to have generally a better prognosis [1217].

Based on a large SWOG 9346 cohort, the PSA level after seven months of ADT was used to create three prognostic groups (Table 6.6.2) [1218]. A PSA ≤ 0.2ng/mL at seven months has been confirmed as a prognostic marker for men receiving ADT for metastatic disease in the CHAARTED study independent of the addition of docetaxel [1219]. Similarly, reaching PSA levels of ≤ 0.1ng/ml after six months were shown to be correlated with long-term outcomes in the LATITUDE study [1220]. Also for patients treated with ADT and apalutamide, a deep PSA decline defined by ≥ 90% from baseline or to PSA ≤ 0.2ng/mL at a landmark of three months was associated with longer OS [1221] for patients. An SR and meta-analysis confirmed that PSA response following initiation of ADT plus ARPI is strongly associated with OS across all stages of advanced PCa, including mHSPC, nmCRPC, and mCRPC. Achieving undetectable PSA levels or PSA decline of ≥ 90% was consistently associated with prolonged OS, underscoring PSA response as a robust early prognostic biomarker, although its role as a surrogate endpoint for OS remains to be validated [1222].

Table 6.6.1: Definition of high and low volume in CHAARTED [1213-1215] **and high and low risk in LATITUDE** [1173]

	High	**Low**
CHAARTED (volume)	≥ 4 bone metastases including ≥ 1 outside vertebral column or pelvis **AND/OR** Visceral metastasis*	Not high

LATITUDE (risk)	≥ 2 high-risk features of: • ≥ 3 Bone metastasis • Visceral metastasis • ≥ ISUP GG 4	Not high

**Lymph nodes are not considered as visceral metastases.*

Table 6.6.2: Prognostic factors based on the SWOG 9346 study [1218]

PSA after 7 months after start of ADT	Median survival on ADT monotherapy
< 0.2ng/mL	75 months
0.2 ≤ 4ng/mL	44 months
> 4ng/mL	13 months

6.6.4 First-line hormonal treatment

Primary ADT has been the standard of care for over 50 years [1223]. No high-level evidence is available in favour of a specific type of ADT for oncological outcomes - neither for orchiectomy, nor for a LHRH agonist or antagonist. The level of testosterone is reduced much faster with orchiectomy and LHRH antagonist; therefore, they are recommended in patients with impending spinal cord compression or other potential impending complications.

Cardiovascular side effects may be less frequent in patients treated with LHRH antagonists than patients treated with LHRH agonists [1160, 1224-1226]. Therefore, LHRH antagonists may be preferred in patients with pre-existing cardiovascular disease or other cardiovascular risk factors.

6.6.4.a Non-steroidal anti-androgen monotherapy

Older generation non-steroidal anti-androgen (NSAA) monotherapy is inferior to ADT (either medical or surgical) in terms of OS, clinical progression, treatment failure and treatment discontinuation due to AEs [1227] and is generally not recommended. For combination treatment of mHSPC ADT is the standard of care.

6.6.4.b Intermittent versus continuous androgen deprivation therapy

Three independent reviews [1228-1230] and two meta-analyses [1231, 1232] looked at the clinical efficacy of intermittent androgen deprivation (IAD) therapy. All these reviews included eight RCTs, of which only three were conducted in patients with exclusively M1 disease.

So far, the SWOG 9346 is the largest trial addressing IAD in M1b patients [1233]. Of 3,040 screened patients, only 1,535 patients met the inclusion criteria. This highlights the fact that only about 50% of M1b patients can be expected to be candidates for IAD, i.e. the best PSA responders. This was a noninferiority trial leading to inconclusive results: the actual upper limit was above the prespecified 90% upper limit of 1.2 (HR: 1.1, CI: 0.99–1.23), the prespecified noninferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, based on this study, inferior survival with IAD cannot be completely ruled out, even in this highly selected subgroup. The use of intermittent ADT has been superseded as continuous ADT based combination therapy has become SOC.

6.6.4.c Early versus deferred androgen deprivation therapy

Early treatment before the onset of symptoms is recommended in the majority of patients with metastatic hormone-sensitive disease. A Cochrane analysis from 2019 regarding the topic concluded that early ADT probably extends time to death of any cause and time to death from PCa [1234], but the analysis included only a very limited number of metastatic patients. Randomised phase III data is lacking in this specific setting and specifically not with the combination therapies that are standard nowadays, however, data is accumulating for the use of long-term ADT earlier in the disease pathway.

Delaying ADT, often using highly sensitive imaging techniques like PSMA-PET/CT or whole bode MRI, in order to offer RT/SABR for men with oligometastatic PCa is the focus of multiple studies (see Section 6.6.7) [1235].

6.6.5 Combination therapies

All of the following combination therapies have been studied with continuous ADT, not intermittent ADT.

6.6.5.a 'Combined' androgen blockade with older generation NSAA (bicalutamide, flutamide, nilutamide)

Systematic reviews have shown that combined androgen blockade using a NSAA appears to provide a small survival advantage (< 5%) versus monotherapy (surgical castration or LHRH agonists) [1236, 1237]. This minimal survival advantage must be balanced against the increased side effects, especially because the newer combination therapies are more effective as shown specifically for enzalutamide, which was tested against NSAA in phase III trials [1238, 1239].

6.6.5.b Androgen deprivation combined with other agents

6.6.5.b.1 Combination with an ARPI alone (abiraterone, apalutamide, enzalutamide, rezvilutamide, darolutamide)

Two large RCTs (STAMPEDE, LATITUDE), assessed the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with mHSPC [1173, 1240, 1241] (Table 6.6.3). The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit. In LATITUDE with only *de novo* high-risk metastatic patients included, the HR reached 0.62 (0.51–0.76) [1173]. The HR in STAMPEDE was very similar, with 0.63 (0.52–0.76) in the total patient population (metastatic and nonmetastatic) and an HR of 0.61 in the subgroup of metastatic patients [1240]. While only high-risk patients were included in the LATITUDE trial, a post-hoc analysis from STAMPEDE showed the same benefit whatever the risk or the volume category was [1242].

All secondary objectives, such as PFS, time to radiographic progression, time to pain, or time to chemotherapy, were in favour of the combination. No difference in treatment-related deaths was observed with the combination of ADT plus AAP compared to ADT monotherapy (HR: 1.37 [0.82–2.29]). However, twice as many patients discontinued treatment due to toxicity in the combination arms in STAMPEDE (20%) compared to LATITUDE (12%) [1241]. Based on these data upfront AAP combined with ADT has become a standard option in men presenting *de novo* metastatic PCa.

In five large RCTs, the addition of AR antagonists to ADT in men with mHSPC was tested [1171, 1172, 1238]. In ARCHES, the primary endpoint was rPFS which was significantly improved for the combination of enzalutamide and ADT (HR 0.39; 95% CI 0.3–0.5). Approximately 36% of the patients had low-volume disease: approximately 25% had prior local therapy and 18% of the patients had received prior docetaxel. In the final prespecified analysis, the key secondary endpoint OS was significantly improved (HR 0.66; 95% CI 0.53-0.81) and a significant benefit for rPFS was maintained (HR 0.63; 95% CI 0.52–0.76) [1243].

In ENZAMET, the primary endpoint was OS. The addition of enzalutamide to ADT in the first analysis improved (HR 0.67; 95% CI 0.52–0.86) compared to ADT plus a non-steroidal antiandrogen. Approximately half of the patients had concomitant docetaxel: about 40% had prior local therapy and about half of the patients had low-volume disease [1172]. In a planned later analysis with a median follow-up of 68 months, the OS benefit of adding enzalutamide was maintained (HR 0.7 95% CI 0.58-0.84) (Table 6.6.4) [1244].

In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were co-primary endpoints. In the primary analysis, rPFS was significantly improved through the addition of apalutamide (HR 0.48; 95% CI 0.39–0.6). OS at 24 months was improved for the combination (HR 0.67; 95% CI 0.51–0.89). In the final analysis, the HR for OS was 0.65 (0.53–0.79) without adjustment for crossover. In this trial, 16% of patients had prior local therapy, 37% had low-volume disease, and 11% received prior docetaxel [1171, 1245] (Table 6.6.4). A secondary analysis of the Titan study found that nearly half of the patients developing subsequent radiographic progression had no concomitant PSA progression, suggesting that heavy reliance on PSA monitoring may be inadequate for assessing disease activity in this context [1246].

In the CHART trial, ADT plus rezvilutamide was evaluated versus ADT plus bicalutamide in patients with high-volume *de novo* metastatic disease. Ninety percent of the patients were recruited in China. Overall survival and rPFS were co-primary endpoints. At the preplanned interim analysis, rezvilutamide significantly improved rPFS compared with bicalutamide (HR 0.44; 95% CI 0.33–0.58) and OS (HR 0.58; 95% CI 0.44–0.77) (Table 6.6.5) [1239]. Patient reported outcomes as assessed by FACT-P and BPI-SF were superior in men receiving rezvilutamide compared to bicalutamide, delaying both deterioration of pain and the FACT-P functional status [1247].

In ARANOTE, darolutamide plus ADT was randomised 2:1 versus placebo plus ADT. It proved to significantly improve rPFS, which was the primary endpoint (HR 0.54; 95% CI 0.41-0.71], with consistent benefits across subgroups, including high- and low-volume disease [1174]. Adverse events were similar in the two groups. Overall survival was not statistically different in the final analysis (HR 0.81; 95% CI 0.59-1.12) (Table 6.6.5) [1174].

In summary, the addition of the new AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients had *de novo* metastatic disease. The effect in the subgroup analyses seemed to be consistent and therefore, a combination should also be offered for men progressing after radical local therapy [1244, 1248, 1249].

Table 6.6.3: Results from the STAMPEDE arm G and LATITUDE studies

	STAMPEDE [1240]		**LATITUDE** [1173]	
	ADT	ADT + AA + P	ADT + placebo	ADT + AA + P
N	957	960	597	602
Newly diagnosed N+	20%	19%	0	0
Newly diagnosed M+	50%	48%	100%	100%
Key inclusion criteria	Patients scheduled for long-term ADT • newly diagnosed M1 or N+ situations • locally advanced (at least two of cT3 cT4, ISUP grade ≥ 4, PSA ≥ 40ng/mL) • relapsing locally treated disease with a PSA > 4ng/mL and a PSA-DT < 6 mo. or PSA > 20ng/mL or nodal or metastatic relapse		Newly diagnosed M1 disease and 2 out of the 3 risk factors: ISUP GG ≥ 4, ≥ 3 bone lesions, measurable visceral metastasis	
Primary objective	OS		OS; rPFS	
Median follow-up	40 mo.		30.4 mo.	
3-yr. OS	83% (ADT + AA + P) 76% (ADT)		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.63 (0.52-0.76)		0.62 (0.51-0.76)	
M1 only				
N	1,002		1,199	
3-yr. OS	NA		66% (ADT + AA + P) 49% (ADT + placebo)	
HR (95% CI)	0.61 (0.49-0.75)		0.62 (0.51-0.76)	
HR	FFS (biological, radiological, clinical or death): 0.29 (0.25-0.34)		rPFS: 0.49 (0.39-0.53)	

AA = abiraterone acetate; ADT = androgen deprivation therapy; CI = confidence interval; FFS = failure-free survival; HR = hazard ratio; ISUP = International Society of Urological Pathology; mo. = months; N = number of patients; NA = not available; OS = overall survival; P = prednisone; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time; rPFS = radiographic progression-free survival.

Table 6.6.4: Results from the ENZAMET and TITAN studies with OS as primary endpoint

	ENZAMET [1238, 1244]		**TITAN** [1171, 1245]	
	ADT+ older antagonist ± docetaxel (SOC)	ADT + enzalutamide ± docetaxel	ADT + placebo	ADT + apalutamide
N	562	563	527	525
Newly diagnosed M+	72.1%	72.5%	83.7%	78.3%
Low volume	47%	48%	36%	38%
Primary objective	OS		OS; rPFS	
Median follow up	68 mo.		30.4 mo.	
OS	5-year survival: 67% (ADT + enzalutamide) 57% (SOC)		2-yr survival: 84% (ADT + apalutamide) 74% (ADT + placebo)	
HR (95% CI) for OS	0.70 (0.58-0.84)		0.67 (0.51-0.89)	

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mo. = months; N = number of patients; PSA-DT = prostate-specific antigen doubling time; OS = overall survival; rPFS = radiographic progression-free survival; SOC = standard of care; yr. = years.

Table 6.6.5: Results from the ARCHES, CHART and ARANOTE studies

	ARCHES [1172, 1243]		**CHART** [1239]		**ARANOTE** [1174]	
	ADT ± docetaxel	ADT + enzalutamide ± docetaxel	ADT + bicalutamide	ADT + rezvilutamide	ADT+ darolutamide	ADT + placebo
N	576	574	328	326	448	223
Newly diagnosed M+	63%	70%	100%	100%	71.1%	75.3%
Low volume	35%	38%	0%	0%	29.4%	29.6%
Use of early docetaxel	18% (previous)	18% (previous)	0%	0%	0	0
Primary endpoint(s)	rPFS		OS; rPFS		rPFS	
Median follow-up	44.6 mo.		29.3 mo.		25.3 mo.	25.0 mo.
Median rPFS	38.9 mo.	49.8 mo.	23.5 mo.	Not reached	Not reached	25.0 mo.
HR (95% CI) for rPFS	0.63 (0.52-0.76)		HR: 0.46 (0.36-0.60)		0.54 (0.41-0.71)	
Median OS	Not reached	Not reached	Not reached	Not reached	Not reached	
HR (95% CI) for OS	0.66 (0.53-0.81): Main secondary endpoint		0.58 (0.44-0.77)		0.78 (0.58 – 1.05)	

ADT = androgen deprivation therapy; HR = hazard ratio; mo. = months; N = number of patients; OS = overall survival; rPFS = radiographic progression-free survival.

6.6.5.b.2 Androgen deprivation therapy combined with chemotherapy

Three large RCTs were conducted [775, 1088, 1114]. All trials compared ADT alone as the SOC with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks within three months of ADT initiation). The primary objective in all three studies was to assess OS.

In the GETUG 15 trial, all patients had M1 PCa, either *de novo* or after a primary treatment [1250]. They were stratified based on previous treatment and Glass risk factors [1210]. In the CHAARTED trial, the same inclusion criteria applied, and patients were stratified according to disease volume [1213].

STAMPEDE is a multi-arm multistage trial in which the reference arm (ADT monotherapy) included 1,184 patients. One of the experimental arms was docetaxel combined with ADT (n = 593), another was docetaxel combined with zoledronic acid (n = 593). Patients were included with either M1 or N1 or having two of the following three criteria: T3/4, PSA ≥ 40ng/mL or ISUP GG 4–5. Relapsed patients after local treatment were also included if they met one of the following criteria: PSA ≥ 4ng/mL with a PSA-DT < 6 months or a PSA ≥ 20ng/mL, N1 or M1. No stratification was used regarding metastatic disease volume (high/low volume) [891].

In all three trials, toxicity was mainly haematological with approximately 12–15% grade 3–4 neutropenia, and 6–12% grade 3–4 febrile neutropenia. The use of granulocyte colony-stimulating factor receptor (GCSF) was shown to be beneficial in reducing febrile neutropenia. Primary or secondary prophylaxis with GCSF should be based on available guidelines [1251, 1252].

Docetaxel in all three trials was used at the standard dose of 75mg/sqm every three weeks, six cycles in CHAARTED and STAMPEDE and up to nine cycles in GETUG-AFU-15. In subgroup analyses from GETUG-AFU 15 and CHAARTED, the beneficial effect of the addition of docetaxel to ADT was most evident in men with *de novo* metastatic high-volume disease [1214, 1215], while it was in the same range whatever the volume in the post-hoc analysis from STAMPEDE [1253]. The effect of adding docetaxel was less apparent in men who had prior local radical treatment although the numbers were small and the event rates low. An SR and meta-analysis which included these 3 trials showed that the addition of docetaxel to SOC improved survival [1252]. The HR of 0.77 (95% CI: 0.68–0.87, p < 0.0001) translates into an absolute improvement in four-year survival of 9% (95% CI: 5–14). An SR and meta-analysis of individual participant data from the three trials showed that there is no meaningful beneficial effect of addition of docetaxel to ADT for patients with metachronous low volume disease. The largest absolute improvement at five years was observed for the patients with high

volume and clinical stage 4 disease [1254]. Therefore, adding docetaxel alone to ADT should only be considered if no ARPI is available or all available ARPIs are contraindicated.

Triplet therapy: ADT and chemotherapy +/- ARPI

The addition of abiraterone to ADT and docetaxel improved rPFS and OS in the PEACE-1 trial [1255, 1256]. The trial has a 2x2 factorial design and participants with *de novo* (synchronous) metastatic PCa were randomised to standard of care (SOC), which was ADT at the beginning of the trial, later ADT plus docetaxel for six cycles (if chemotherapy-fit) versus SOC plus RT versus SOC plus abiraterone versus SOC plus RT plus abiraterone. Co-primary endpoints were rPFS and OS, which were both significantly improved in the total population. Also in the group of patients who received ADT plus docetaxel as SOC (n = 710), both rPFS and OS were increased with a HR: 0.5 (0.34–0.71) and 0.75 (0.59–0.95), respectively. Of note in this population, about 35% had low-volume disease. Toxicity was modestly increased by the addition of abiraterone, mainly hypertension.

In the ARASENS phase III trial, all patients received ADT and docetaxel for six cycles as SOC plus darolutamide or placebo [1257]. A total of 1,306 metastatic patients were included, 14% of them with relapsed disease after radical local treatment (metachronous). The primary endpoint was OS, and this was statistically significantly improved by the addition of darolutamide (HR: 0.68; 95% CI: 0.57–0.8).

In this trial the occurrence of AEs was similar in both arms. Of the included patients 77% had high volume and 70% high-risk disease. In an unplanned subgroup analysis the beneficial effect of adding darolutamide versus placebo for OS was seen in the patients with high-volume (HR 0.69; 0.57-0.82), with high-risk (HR: 0.71; 0.58-0.86) and in low-risk disease (HR: 0.62; 0.42-0.9), for the small subgroup of patients with low-volume disease the results were less clear regarding an OS benefit (HR: 0.68; 0.41-1.13) [1258].

In both PEACE I and ARASENS, docetaxel and the ARPI were given concomitantly. In ENZAMET, ENZAMET about 45% of patients received concurrent docetaxel, in TITAN and ARCHES, 11-18% of patients received prior docetaxel as a part of SOC [1171, 1172, 1238, 1243-1245].

ADT and ARPI +/- PARPI (AMPLITUDE)

The AMPLITUDE phase III trial (n = 696) evaluated the combination of the PARP inhibitor niraparib with abiraterone acetate plus prednisone (AAP) in patients with mHSPC with germline or somatic alterations in HRR genes, including BRCA1 or BRCA2 or at least one of seven other HRR genes [1259]. The primary endpoint was met, with a significant improvement in rPFS observed in the BRCA subgroup (HR 0.52; 95% CI: 0.37–0.72) and in the intention-to-treat population (HR 0.63; 95% CI: 0.49–0.80).

The secondary endpoint of OS was immature (HR 0.79) and showed a trend towards favouring niraparib. More grade 3–4 AEs were reported in the niraparib arm: 75% versus 59%, especially anaemia (29% vs. 4.6%), hypertension (26.5% vs. 18.4%) and the need of transfusion. The treatment was more likely to be discontinued in the niraparib arm where also one case of MDS was reported.

ADT and ARPI +/- AKT inhibitor (CAPItello-281)

The phase III RCT CAPItello-281 trial evaluated the addition of the AKT inhibitor capivasertib to standard therapy with abiraterone plus ADT in patients with de novo PTEN deficient mHSPC [1260]. Central testing of 6,003 pre-screened patients confirmed immunohistochemical (IHC) ≥ 90% PTEN loss in 1,519 (25.3%) assessed specimens. Of 1,012 included patients 507 were randomised to capivasertib plus abiraterone and 505 to placebo plus abiraterone with both arms receiving concomitant prednisone/prednisolone and ADT.

The primary endpoint of rPFS was significantly improved by capivasertib versus placebo (median 33.2 vs. 25.7 months; HR: 0.81; 95% CI: 0.66–0.98, p < 0.034. The secondary endpoint of OS was still immature (HR: 0.90; 95% CI: 0.71–1.15, p = 0.401).

*6.6.6 **Treatment selection and patient selection***

Selecting patients for triplets of either docetaxel, niraparib or capivasertib in addition to ADT and ARPI is challenging. The addition of docetaxel was not formally tested against ADT and ARPI and only tested in the setting of ARPI in addition to ADT and docetaxel. The addition of niraparib or capivasertib requires upfront molecular and IHC testing and has been shown to improve rPFS but not OS.

In men with *HRR* mutations, especially in those with *BRAC* 1 or 2 alterations, the addition of niraparib to ADT and abiraterone plus prednisolone appears to be an important new option for this poor prognostic group of patients. Regulatory approval of this combination is pending.

The OS benefit of adding docetaxel to ADT and ARPI has not been studied directly and ADT plus ARPI remains the SOC in patients with no documented deficiency of *HRR* or *PTEN*. However, *PTEN* transcriptomic inactivity as assessed by NGS of RNA, revealed shorter OS on ADT and abiraterone, but not with ADT and docetaxel, suggesting a higher docetaxel benefit in men with *PTEN* inactive PCa [1261]. Ideally, the transcriptomic *PTEN* activity should be known when counselling patients with mHSPC. Of note, IHC based *PTEN* loss and transcriptomic *PTEN* inactivity were not well aligned as 30% of those with *PTEN* positivity by IHC were classified as transcriptomically *PTEN* inactive.

For patients without the above mentioned molecular aberrations the choice of treatment is between ADT plus ARPI and the addition of docetaxel for six cycles. Several network meta-analyses of the published data have concluded that combination therapy is more efficient than ADT alone, but none of the doublet combination therapies have been convincingly proven to be superior over another [1261-1266]. In an SR and meta-analysis looking at association between age and efficacy of combination therapy, patients appeared to benefit from combination therapy irrespective of age [1266]. As a consequence, patients should be offered combination treatment unless there are clear contra-indications or they present with asymptomatic disease and a very short life expectancy (based on frailty assessment or non-cancer comorbidities).

Docetaxel as sole addition to ADT is no longer recommended in the majority of patients if an ARPI is available and there are no contra-indications to use one. The different ARPIs are similar regarding efficacy, but differ regarding their toxicity profiles. The choice of an ARPI should be based on the individual patient's risk profile and comorbidities [1267]. For patients with metachronous low-volume PCa, ARPI doublet therapies were ranked as the potentially most efficacious treatment option and the expected outcomes were not significantly different from those achieved by triplet regimens; however, docetaxel adds toxicity [1261].

The question whether triplet therapy is superior to ADT and ARPI doublet therapy has been addressed by multiple SRs and meta-analyses. The choice between triplet therapy and the ADT and ARPI doublet therapy should be discussed with *de novo* and/or high-volume/high-risk disease patients [1268-1270].

6.6.7 ***Treatment of the primary tumour in newly diagnosed metastatic disease***

The first reported trial evaluating prostate RT in men with mHSPC was the HORRAD trial. Four hundred and thirty-two patients were randomised to ADT alone or ADT plus IMRT with IGRT to the prostate. Overall survival was not significantly different (HR: 0.9 [0.7–1.14]) and median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63–0.97]) [1271]. The risk of obstructive PCa–related local symptoms such as bladder outlet obstruction or hydronephrosis was reduced in men who underwent RT as evidenced by interventions required in 18% vs. 30% (HR 0.61 [0.37–0.99]) after a median follow-up time of 75 months for patients who are still alive (66/328).

The STAMPEDE trial evaluated 2,061 men with mHSPC who were randomised to ADT alone versus ADT plus RT to the prostate. This trial confirmed that RT to the primary tumour did not improve OS in unselected patients [1216]. However, following the results from CHAARTED and prior to analysing the data, the original screening investigations were retrieved, and patients categorised as low or high volume. In the low-volume subgroup (n = 819), there was a significant OS benefit by the addition of prostate RT. This was confirmed by the latest analysis of long-term follow-up (median follow-up of 61 months [HR: 0.64 for OS benefit in the low-volume group]) [1272].

A secondary, not preplanned analysis of the STAMPEDE trial confirmed the benefit of prostate RT in patients with ≤ 3 bone metastases, but also showed a benefit in patients with M1a disease [1273]. No evidence of difference in time to symptomatic local events was found with median follow-up of over five years [1272].The dose used in these indications should be equivalent of up to 72Gy in 2Gy fractions. Therefore, RT of the prostate only in patients with low-volume metastatic disease should be considered. In an SR and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81–1.04, p = 0.195) [1274]. However, there was a clear difference in the effect of metastatic burden on survival with an absolute improvement of 7% in three-year survival in men who had four or fewer bone metastases.

The randomised phase-III PEACE-1 trial with a 2x2 factorial design (SOC, SOC + abiraterone, SOC + RT and SOC + abiraterone + RT) demonstrated that adding prostate RT (total dose 74Gy in 37 fractions) significantly prolonged the co-primary endpoint of PFS from 4.4 years to 7.5 years in the low-volume metastatic burden group treated with SOC+ARPI. Additionally, a significant delay in the time to castration resistance was observed, although there was no improvement in OS in this group [1275].

PEACE-1 also reported a significant reduction in the incidence of serious genitourinary events such as obstruction, bleeding, insertion of double-J stent and TURP for patients treated with local RT to the prostate. This was an important secondary endpoint in the PEACE-1 study where the preventive effect of RT was observed both in the cohort of patients with low-volume metastatic disease (26% vs. 11%; delay in the time to first serious genitourinary event p = 0·0002;) and the overall cohort (22.3% vs 12.2%; p = 0·0001) [1275].

A network meta-analysis of ten RCTs, including PEACE-1, in a population with *de novo* mHSPC and no prior docetaxel use, did not reveal a significant OS benefit for the addition of RT to SOC plus ARPI versus SOC plus ARPI alone (HR 0.76; 95% CI 0.51–1.16) [1276].

*6.6.8 **Metastasis-directed therapy in M1 patients***

In patients relapsing after a local treatment, a metastases-directed therapy (MDT) has been proposed, with the aim to delay systemic treatment. The same rationale can be applied in men with a single or only few metastases at diagnosis, i.e., oligometastatic disease. The definition of oligometastatic PCa varies and depends strongly on the applied imaging [1235].

A retrospective analysis on 211 patients treated with MDT aimed at defining prognostic factors for MFS, palliative ADT-free (pADT) survival and cause-specific survival (CSS). With a median follow-up of 42 months after MDT, patients with cN1 only had significantly superior five-year MFS, pADT and CSS when compared to patients with M1 disease (p<0.02). At five years, 23% of patients were free of BCR [1277].

Two randomised phase II trials assessed MDT using surgery ± SABR versus surveillance [1100] or SABR versus surveillance in men with oligo-recurrent PCa [1278]. Oligo recurrence was defined as < 3 lesions on choline PET/CT only [1100] or conventional imaging with MRI/CT and/or bone scan [1278]. The sample size was small with 62 and 54 patients, respectively, and a substantial proportion of them had nodal disease only [1100]. Androgen deprivation therapy-free survival was the primary endpoint in the STOMP study which was longer with MDT than with surveillance [1100]. The primary endpoint in the ORIOLE trial was progression after six months which was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [1278].

The combined results of STOMP and ORIOLE confirmed the significant improvement in PFS in favour of MDT (HR: 0.44, p < 0.001) [1279].

A phase II trial assessed the biochemical response after ^{18}F-DCFPyL PET/MRI and subsequent MDT. Overall biochemical response rate, defined as ≥ 50% PSA decline, was 60%, including 22% of patients with complete biochemical response [1280].

The randomised phase II EXTEND trial investigated whether MDT, when added to SOC systemic treatment, improved PFS when compared to SOC systemic treatment alone in oligometastatic PCa patients, with oligometastatic being defined as maximally five lesions. In total, 87 patients were randomised and the vast majority presented with one or two metastatic lesions. In total, 51 patients received ADT alone, while 36 patients also received ARPI. The addition of MDT significantly improved both PFS (15.8 months vs. not reached; HR: 0.25; p<0.001) and eugonadal PFS (6.1 months vs. not reached; HR: 0.32; p = 0.03). This significant benefit was observed both in the patient group receiving ADT alone or ADT + ARPI [1281]. In analogy, the SATURN trial, which included 28 oligo-recurrent metastatic PCa patients, looked at the PFS of adding dual ARPI and MDT to existing ADT. The median PFS in SATURN was 19.3 months and 50% of the patients still had an undetectable PSA 6 months after testosterone recovery. While MDT-induced toxicity was very low, adding dual ARPI induced grade 3 toxicity in 20% of the patients [1282].

Five-year outcomes of SBRT for oligometastatic PCa from the prospective TRANSFORM phase II trial have been reported [1283]. In total 199 men (stage M1a/b and/or N1) received SBRT and 76% were hormone naïve at baseline. The primary endpoint was five-year treatment escalation free survival (TE-FS), defined as freedom from any new cancer therapy other than further SBRT for up to five lesions. Ninety-three percent had prior RP, 46% of the patients had stage N1 only, 76% were staged by PET-CT. The rate of five-year TE-FS was 21.7% (CI: 15.7%-28.7%) overall. These data suggest that SBRT based MDT may be an effective option for delaying systemic treatment escalation in highly selected patients.

The randomised phase II clinical trial (RADIOSA) investigated whether six months ADT added to SBRT versus SBRT alone for hormone-sensitive metachronous oligo-recurrent PCa improved clinical PFS [1284]. In total, 105 patients were randomised, 52 to SBRT alone and 53 to SBRT + ADT, three patients were lost to follow up. With a median follow up of 31 months the clinical PFS was 15.1 months for the SBRT-group (95% CI: 12.4-22.8) versus 32.2 months for the SBRT+ADT group (22.4-not reached; HR: 0.43 0.26-0.72, p = 0.0010). No grade > 2 late ADT- or SBRT-related toxicities were reported.

Currently there are no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as investigational until the results of ongoing RCTs are available [1285, 1286]. The toxicity of MDT is low, with almost no grade ≥ 3 toxicity [1287-1289].

6.6.8 Recommendations for the first-line treatment of hormone-sensitive metastatic disease*

Recommendations	Strength rating
First-line treatment	
Discuss all patients with hormone-sensitive metastatic disease in a multidisciplinary team	Strong
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting luteinising hormone-releasing hormone (LHRH) agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
At the start of ADT, offer LHRH antagonists or orchiectomy to patients with impending clinical complications, such as spinal cord compression or bladder outlet obstruction.	Strong
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy (≥ 1 year) and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide or rezvilutamide to patients with M1 disease who are fit for the regimen.	Strong
Offer ADT combined with darolutamide to patients with M1 disease who are fit for the regimen	Weak
Offer docetaxel only in combination with ADT plus abiraterone or darolutamide to patients with M1 disease who are fit for docetaxel.	Strong
Test patients for somatic or germline homologous recombination repair aberrations, since they may qualify for the addition of niraparib to ADT plus abiraterone in patients with M1 disease.	Weak
Offer ADT combined with prostate radiotherapy (using doses up to the equivalent of 72 Gy in 2 Gy fractions) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or a well-designed prospective cohort study.	Strong
Supportive care	
Assess osteoporosis risk factors and perform a dual emission X-ray absorptiometry scan when commencing long-term ADT, to mitigate osseous complications.	Strong
Offer bone protection to avoid fractures in patients receiving combination treatment.	Strong
Offer calcium and vitamin D supplementation when prescribing either denosumab or bisphosphonates and monitor serum calcium.	Strong
Treat painful bone metastases early on with palliative measures, such as radiotherapy and adequate use of analgesics.	Strong

In patients with spinal cord compression, start immediate high-dose corticosteroids and assess for spinal surgery, potentially followed by radiation. Offer radiation therapy alone if surgery is not appropriate.	Strong

**All the following statements are based on metastatic disease defined by bone scintigraphy and CT scan/MRI.*

6.7 Treatment: Castration-resistant PCa (CRPC)

*6.7.1 **Definition of CRPC***

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL.
b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan, ideally confirmed [1290], or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [1291]. Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.
c. Unequivocal clinical progression.

*6.7.2 **Management of mCRPC - general aspects***

Selection of treatment for mCRPC is multifactorial and in general dependent on:

- previous treatment for mHSPC and for non-mHSPC;
- previous treatment for nmCRPC and mCRPC;
- quality of response and pace of progression on previous treatment;
- known cross resistance between androgen receptor pathway inhibitor (ARPI);
- co-medication and known drug interactions (see approved summary of product characteristics);
- known genetic alterations and microsatellite instability–high (MSI-H)/mismatch repair-deficient (*dMMR*) status;
- known histological variants and DNA repair deficiency (to consider platinum or targeted therapy like PARPi);
- local approval status of drugs and reimbursement situation;
- available clinical trials;
- the patient and his comorbidities.

6.7.2.a Molecular diagnostics

Metastatic patients should be offered somatic genomic testing for homologous repair and MMR defects early on. Testing can be performed on more recently collected primary tumour tissue or on tissue from metastases. Alternatively, but still less common, genetic testing on circulating tumour DNA (ctDNA) is an option and has been used in some trials. One test, the FoundationOne® Liquid CDx, has been FDA approved [1292]. Defective *MMR* assessment can be performed by IHC for *MMR* proteins (*MSH2, MSH6, MLH1* and *PMS2*) and/or by next generation sequencing (NGS) assays [1195]. Germline testing for at least *BRCA1/2, ATM* and *MMR* is recommended for patients with high-risk localised PCa and particularly for patients with metastatic PCa.

Molecular diagnostics should be performed by a certified (accredited) institution using a standard NGS multiplication procedure (minimum depth of coverage of 200 X). The genes and respective exons should be listed; not only DNA for mutations but RNA needs to be examined for fusions and protein expression to obtain all clinically relevant information. A critical asset is the decision support helping to rate the mutations according to their clinical relevance [1193, 1194].

Level 1 evidence for the use of PARP inhibitors has been reported [341, 1196-1207]. Microsatellite instability (MSI) high (or *MMR* deficiency) is rare in PCa, but for those patients, pembrolizumab has been approved by the FDA and could be a valuable additional treatment option [1187, 1208].

*6.7.3 **Treatment decisions and sequence of available options***

Approved agents for the treatment of mCRPC in Europe are docetaxel, abiraterone/prednisolone (AAP), enzalutamide, cabazitaxel, olaparib, niraparib/AAP, talazoparib/enzalutamide, radium-223 and lutetium (177Lu) vipivotide tetraxetan. For nmCRPC, apalutamide, darolutamide and enzalutamide have been approved. In general, sequencing of ARPIs like abiraterone and enzalutamide is not recommended particularly if the time of response to ADT and to the first ARPI was short (≤six to twelve months) and high-risk features of rapid progression are present 1293-1295].

The use of chemotherapy with docetaxel and subsequent cabazitaxel in the treatment sequence is recommended and should be applied early enough when the patient is still fit for chemotherapy. This is supported by high-level evidence [1293].

In case of a known BRCA alteration, the use of a PARP inhibitor should always be prioritised as these patients harbour an adverse prognosis and don't respond well to most other treatments. PARP inhibitor use significantly improves rPFS and OS in these patients [1296-1299].

*6.7.4 **Non-metastatic CRPC***

Frequent PSA testing in non-metastatic men treated with ADT has resulted in earlier detection of biochemical progression. Of these men approximately one-third will develop bone metastases within two years, detected by conventional imaging [1014].

In men with CRPC and no detectable clinical metastases using bone scan and CT scan, baseline PSA level, PSA velocity and PSA-DT have been associated with time to first bone metastasis, bone MFS and OS [1014, 1300]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group suggested a bone scan and a CT scan when the PSA reached 2ng/mL and if this was negative, it should be repeated when the PSA reached 5ng/mL, and again after every doubling of the PSA based on PSA testing every three months in asymptomatic men [1301]. Symptomatic patients should undergo relevant investigations regardless of PSA level. With more sensitive imaging techniques like PSMA hybrid imaging or whole-body MRI, more patients are diagnosed with early mCRPC [1302]. It remains unclear if the use of PSMA PET/CT in this setting improves outcome.

Three large phase III RCTs, PROSPER [1303], SPARTAN [1304] and ARAMIS [1305], evaluated MFS as the primary endpoint in patients with nmCRPC (M0 CRPC) treated with enzalutamide (PROSPER) vs. placebo or apalutamide (SPARTAN) vs. placebo or darolutamide (ARAMIS) versus placebo, respectively (Table 6.7.1). The M0 status was established by CT and bone scans. Only patients at high risk for the development of metastasis with a short PSA-DT of ≤ 10 months were included. Patient characteristics in the trials revealed that about two-thirds of participants had a PSA-DT of < 6 months. All trials showed a significant MFS benefit. All three trials showed a survival benefit after a follow-up of more than 30 months. In view of the long-term treatment with these AR targeting agents in asymptomatic patients, potential AEs need to be taken into consideration and the patient informed accordingly.

*6.7.5 **Metastatic CRPC***

The remainder of this section focuses on the management of men with proven mCRPC on conventional imaging.

6.7.5.a Conventional androgen deprivation in CRPC

Eventually men with PCa will show evidence of disease progression despite castration. Two trials have shown only a marginal survival benefit for patients remaining on LHRH analogues during second- and third-line therapies [1306, 1307]. However, in the absence of prospective data, the modest potential benefits of continuing castration outweigh the risk of treatment. In addition, all subsequent treatments have been studied in men with ongoing androgen suppression, therefore, it should be continued in these patients.

*6.7.6 **First-line treatment of metastatic CRPC***

6.7.6.a Abiraterone

Abiraterone was evaluated in 1,088 chemo-naive, asymptomatic or mildly symptomatic mCRPC patients in the phase III COU-AA-302 trial. Patients were randomised to abiraterone acetate or placebo, both combined with prednisone [1308]. Patients with visceral metastases were excluded. The main stratification factors were ECOG PS 0 or 1 and asymptomatic or mildly symptomatic disease. Overall survival and rPFS were the co-primary endpoints. After a median follow-up of 22.2 months there was significant improvement of rPFS (median 16.5 vs. 8.2 months, HR: 0.52, p < 0.001) and the trial was unblinded. At the final analysis with a median follow-up of 49.2 months, the OS endpoint was significantly positive (34.7 vs. 30.3 months, HR: 0.81, 95% CI: 0.70–0.93, p = 0.0033) [1309]. Adverse events related to mineralocorticoid excess and liver function abnormalities were more frequent with abiraterone but mostly grade 1–2. Subset analysis of this trial showed the drug to be equally effective in an elderly population (> 75 years) [1310].

6.7.6.b Enzalutamide

A randomised phase III trial (PREVAIL) included a similar patient population and compared enzalutamide and placebo [1311]. Men with visceral metastases were eligible but the numbers included were small. Corticosteroids were allowed but not mandatory. PREVAIL was conducted in a chemo-naive mCRPC population of 1,717 men and showed a significant improvement in both co-primary endpoints, rPFS (HR: 0.186, CI: 0.15–0.23, $p < 0.0001$), and OS (HR: 0.706, CI: 0.6–0.84, $p < 0.001$). A ≥ 50% decrease in PSA was seen in 78% of patients. The most common clinically relevant AEs were fatigue and hypertension. Enzalutamide was equally effective and well tolerated in men > 75 years [1312] as well as in those with or without visceral metastases [1313]. However, for men with liver metastases, there seemed to be no discernible benefit [1313, 1314].

Enzalutamide has also been compared with bicalutamide 50 mg/day in a randomised double-blind phase II study (TERRAIN) showing a significant improvement in PFS (15.7 months vs. 5.8 months, HR: 0.44, $p < 0.0001$) in favour of enzalutamide [1314]. With extended follow-up and final analysis, the benefit in OS and rPFS were confirmed [1315].

6.7.6.c Docetaxel

A statistically significant improvement in median survival of 2.0–2.9 months has been shown with docetaxel compared to mitoxantrone plus prednisone [1316, 1317]. The standard first-line chemotherapy is docetaxel 75 mg/m^2, three-weekly doses combined with prednisone 5 mg twice a day (BID), up to ten cycles. Prednisone can be omitted if there are contraindications or no major symptoms. The following independent prognostic factors: visceral metastases, pain, anaemia (Hb < 13 g/dL), bone scan progression, and prior estramustine may help stratify the response to docetaxel. Patients can be categorised into three risk groups: low risk (0 or 1 factor), intermediate (2 factors) and high risk (3 or 4 factors), and show three significantly different median OS estimates of 25.7, 18.7 and 12.8 months, respectively [1318].

Age by itself is not a contraindication to docetaxel [1319] but attention must be paid to careful monitoring and comorbidities as discussed in Section 6.1 [1320]. In men with mCRPC who are thought to be unable to tolerate the standard dose and schedule, docetaxel 50 mg/m^2 every two weeks seems to be well-tolerated with less grade 3–4 AEs and a prolonged time to treatment failure [1321].

So far, no combination with docetaxel has proven to be superior to docetaxel alone in unselected mCRPC patients, including the combination with the checkpoint inhibitor pembrolizumab [1322].

6.7.6.d Combinations with PARP inhibitors

Based on the suggestion that there is a synergistic antitumour effect when combining an ARPI with a PARP inhibitor, several such combination trials were conducted in first-line mCRPC patients without prior ARPI use, with different trial designs and different patient- and molecular panel selection.

Abiraterone/prednisone plus olaparib

A randomised double-blind, phase III trial (PROpel) of AAP plus olaparib (300 mg twice daily) or placebo in patients with mCRPC in the first-line setting was conducted [1198, 1199]. Patients (n = 796) were randomly assigned 1:1 to study treatment regardless of homologous recombination repair gene mutation (HRRm) status which was retrospectively evaluated and determined by tumour tissue and circulating tumour DNA tests. The primary end point was imaging-based PFS (ibPFS) by investigator assessment. All patients were ARPI naïve, 24% were docetaxel pretreated. The result was significantly positive in favour of the combination with ibPFS of 24.8 versus 16.6 months (HR 0.66; 95% CI: 0.54 to 0.81; $p = 0.001$). In the prespecified final analyses the key secondary endpoint OS had only 47.9% maturity and did not meet the prespecified two-sided boundary for significance (0.95% CI: 0.81, 0.67-1.0, $p = 0.054$). The exploratory analysis of the subgroup of patients with positive HRRm status showed a rPFS HR of 0.50 (CI: 0.34 to 0.73). The BRCA mutated patients (11% of the ITT population) had an even larger benefit for rPFS (HR 0.24; 95% CI: 0.12 - 0.45) and the OS HR in these patients was 0.30 (95% CI: 0.15 - 0.59), suggesting that the overall benefit observed in the ITT population was primarily driven by patients with a BRCA mutation [1200].

The most common AEs in patients receiving olaparib plus AAP were anaemia (48%; ≥ G3 15%), fatigue (38%), nausea (30%), diarrhoea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%); 18% of patients required at least one blood transfusion and 12% required multiple transfusions [1200]. The combination of olaparib plus AAP was approved by the EMA for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated [1240]. In the US, the FDA has approved olaparib with AAP for mCRPC patients with deleterious or suspected deleterious BRCA mutations as determined by an FDA-approved companion diagnostic test [1201]. For patients without BRCA mutations, the FDA determined that the

modest rPFS improvement, combined with clinically significant toxicities, did not demonstrate a favourable risk/benefit assessment [1297].

The combination of PARP inhibitor plus ARPI in patients with BRCA1/2 (or ATM) mutations in the first-line as opposed to the use of PARP inhibitor monotherapy or the sequential use of these agents is supported by a randomised phase II trial (BRCAAway) albeit with low patient numbers and thus a low level of evidence [1323].

Abiraterone/prednisone plus niraparib

In a randomised, double-blind, phase III trial (MAGNITUDE) AAP plus niraparib 200 mg once/daily or placebo, was evaluated [1202]. The study prospectively included two cohorts, an HRR-negative and an HRR-positive cohort. The HRR-negative cohort was closed early for futility after enrolling 200 patients. In the overall HRR-positive cohort, the addition of Niraparib to AAP resulted in a significant improvement in the first endpoint rPFS compared to AAP plus placebo (HR = 0.73; 95% CI 0.56-0.96; p = 0.0217) and the median rPFS was 16.5 vs. 13.7 months in favour of the combination. In particular, the 113 patients with *BRCA* 1/2 mutations [1203] who received AAP plus niraparib [1203] derived a major rPFS benefit (19.5 vs. 10.9 months; HR = 0.55 [95% CI 0.39-0.78]; nominal p = 0.0007). The final analysis of OS at median follow-up of 37.3 months revealed no difference between niraparib + AAP and placebo + AAP in the HRR+ population (HR 0.931; 95% CI 0.72-1.20; p = 0.585) or the subgroup with BRCA 1/2 alterations (HR 0.788, 95% CI 0.55-1.120 nominal p = 0.183) [1324]. The most common side effects with Niraparib plus AAP in the ITT population were anaemia (46.2%), fatigue (26.4%), hypertension (31.6%) and constipation (30.7%). The combination of niraparib plus AAP in a dual-action tablet has been approved by the EMA and the FDA for patients with mCRPC and BRCA 1/2 mutations in whom chemotherapy is not clinically indicated [1204].

Enzalutamide plus Talazoparib

A randomised double-blind, phase III trial (TALAPRO-2) of the PARP inhibitor talazoparib (0.5mg daily) plus enzalutamide versus enzalutamide/placebo showed a significantly better median rPFS (first endpoint) in favour of the combination regardless of the HRR pathway status [1205]. The median rPFS was 33.1 months [95% CI 27.4–39.0] versus 19.5 months [16.6–24.7], (HR 0.67 [95% CI 0.55–0.81]; p < 0·0001).

For the subgroups of patients with HRR mutations the benefit of the combination was much more pronounced. The HRR gene-mutated population showed a median rPFS of 27.9 (16.6–not reached) for the talazoparib combination versus 16.4 (10.9–24.6) for the placebo group (0.46; 95% CI: 0.30–0.70; p = 0.0003) and 0.70 (0.54–0.89; p = 0.0039) in patients with a status of non-deficient or unknown. In an exploratory analysis, the HR for rPFS in patients with BRCA-mutated mCRPC was 0.23 (0.10–0.53; p = 0.0002) and, in patients with non-BRCAm HRR gene-mutated mCRPC, it was 0.66 (0.39–1.12; p = 0.12) in favour of the talazoparib combination [1205]. At a median follow-up of 52.5 months, OS was significantly improved with talazoparib plus enzalutamide compared with enzalutamide plus placebo (HR 0.80, 95% CI 0.66–0.96; p = 0·016); median OS was 45.8 months in the talazoparib group compared with 37.0 months in the control group. This effect was much more pronounced in HRR-deficient patients (n = 69; HR 0.55 [0.36–0.83]; p = 0·0035) and to a much lesser extent in HRR-non-deficient or unknown patients (n = 636; HR 0.88 [0.71–1.08]; p = 0·22). At the final updated analysis, rPFS showed a slightly higher HR (HR 0.67 [0.55–0.81]; p < 0·0001) [1325].

The most common treatment-emergent adverse events with the addition of talazoparib were anaemia, neutropenia, and fatigue; the most common grade 3–4 event was anaemia (46%), which improved after dose reduction, however, 39% required a blood transfusion, including 22% who required multiple transfusions, 8% discontinued treatment due to anaemia and 2 patients on the combination were diagnosed with myelodysplastic syndrome/acute myeloid leukaemia [1205]. In TALAPRO-2, an HRR-deficient-only cohort (cohort 2; n = 230) was also recruited. The primary analysis for the combined HRR-deficient population (n = 399) met the rPFS endpoint with a HR 0.45 (95% CI, 0.33 to 0.61; p < 0.0001; median not reached at the time of the analysis for the talazoparib group versus 13.8 months for the placebo group). At median follow-up of 44.2 months, talazoparib plus enzalutamide resulted in a statistically significant improvement in OS versus enzalutamide (HR 0.62 [95% CI 0.48–0.81]; two-sided p =0·0005) in this cohort of HRR deficient patients. The median OS was 45.1 months (95% CI 35.4 - not reached) in the talazoparib group versus 31.1 months in the control group. In the subgroup of patients with BRCA 1/2 alterations (n = 155 [39%]), median OS was not reached for talazoparib plus enzalutamide versus 28.5 months for enzalutamide (HR 0.50 [95% CI 0.32–0.78; p =0·0017); four-year OS rates were 53% in the talazoparib group versus 23% in the control group. Updated rPFS favoured talazoparib plus enzalutamide versus enzalutamide (HR 0.47 [95% CI 0.36–0.61]; p < 0·0001; median rPFS was 30.7 versus 12.3 months [1206, 1326]. The expected clinical benefit in the subgroups needs to be weighed against the potential burden of side effects [1296].

The FDA approved talazoparib with enzalutamide only for HRR gene-mutated mCRPC [1207, 1296, 1327]. In May 2025, the FDA's Oncologic Drugs Advisory Committee (ODAC) deemed the results from TALAPRO-2 insufficient to conclude a favourable benefit-risk profile for adding talazoparib to enzalutamide in patients with non-HRRm mCRPC [1328]. The concerns were the lack of a prespecified, statistically powered analysis in the non-HRRm subgroup, which represents the majority of the target population and thus the uncertainty about the reliability of the per se small survival effect in non-HRRm. Concerns regarding increased hematologic toxicity were also raised. The EMA has approved the combination of talazoparib and enzalutamide for the treatment of patients with mCRPC in whom chemotherapy is not clinically indicated [1329]. Regarding additional side effects of special interest, there seems to be a doubling of the risk of thromboembolic events with the use of PARPis. In a meta-analysis of 2,210 and 1,662 patients with PC and PARPi treatment vs. control, PARPi had a statistically significant increased risk of thrombosis in PCa patients (OR = 1.98, 95 % CI: 1.06–3.70, p = 0.030) with 96 (4.3 %) and 37 (2.2 %) in the PARPi and control groups, respectively [1330].

Based on 18 placebo-controlled RCTs (n = 7,307 patients, tumour agnostic), PARPis significantly increased the risk of myelodysplastic syndrome and acute myeloid leukaemia compared with placebo treatment (Peto OR 2·63 [95% CI 1·13–6·14], p = 0·026) with no between-study heterogeneity (I2=0%, x2 p = 0·91). Median treatment duration was 9.8 months (IQR 3·6–17·4; n = 96) and median latency period since first exposure to a PARPi was 17.8 months (8·4–29·2; n = 58). Of 104 cases that reported outcomes, 47 (45%) resulted in death [1331].

Radium-223 in combination with enzalutamide

Men with mCRPC and bone metastases were randomised 1:1 to enzalutamide with or without radium-223 (ENZ vs. ENZ-RAD) in the EORTC 1333/PEACE-3 trial [1332]. After an amendment, co-administration of zoledronic acid or denosumab (bone protecting agents) was obligatory. The primary endpoint was rPFS. Of the 446 enrolled men, 87.9% in the ENZ-RAD arm completed the scheduled six cycles of RAD. Radiographic PFS was 16.4 (95% CI 13.8-19.2) months in the ENZ arm and 19.4 (95% CI 17.1-25.3) months in the ENZ-RAD arm. The HR for rPFS was 0.69 (95% CI 0.54-0.87; p = 0.0009). The HR for OS was 0.69 (95% CI 0.52-0.90; p = 0.0031), with median OS in the preplanned interim analysis of 35.0 (95% CI 28.8-38.9) months in the ENZ arm and 42.3 (95% CI 36.8-49.1) months in the ENZ-RAD arm. Treatment-emergent adverse events (TEAE) ≥ grade 3 were reported in 55.8% and 65.6% of the patients in the ENZ and ENZ-RAD arms, respectively. The most frequent grade ≥ 3 TEAE in the ENZ-RAD arm were hypertension (34%), fatigue (6%), anaemia (5%), and neutropenia (5%). No TEAE ≥ grade 3 was increased by more than 5% in the ENZ-RAD arm versus the ENZ arm.

The interim safety data analysis from the randomised phase III PEACE-3 trial comparing radium-223 combined with enzalutamide for first-line mCPRC to enzalutamide alone showed a high fracture rate in both arms. For patients who received bone protecting agent (BPA) therapy, after it became mandatory on the trial, fracture rates significantly decreased in both study arms one-year fractures decreased from 15.6% to 2.6% with a BPA in patients receiving enzalutamide monotherapy. This underscores the high risk of fracture in patients with mCRPC and the necessity of complying with guidelines regarding BPA administration in the ARPI era [1333].

*6.7.7 **Second-line treatment for mCRPC***

All patients who receive treatment for mCRPC will eventually progress. All treatment options in this setting are presented in Table 6.7.3. There is a paucity of high-level data with regards to the sequence of treatments, particularly in case of pretreatment for mHSPC with ARPI and/or docetaxel or other agents. Treatment sequences will depend on which agents were used previously.

6.7.7.a Cabazitaxel

Cabazitaxel is a taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomised, phase III trial (TROPIC) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy [1334]. Patients received a maximum of ten cycles of cabazitaxel (25 mg/m^2) or mitoxantrone (12 mg/m2) plus prednisone (10 mg/day). Overall survival was the primary endpoint which was significantly longer with cabazitaxel (median: 15.1 vs. 12.7 months, p < 0.0001). There was also a significant improvement in PFS (median: 2.8 vs. 1.4 months, p < 0.0001), objective RECIST response (14.4% vs. 4.4%, p < 0.005), and PSA response rate (39.2% vs. 17.8%, p < 0.0002). Treatment-associated WHO grade 3–4 AEs developed significantly more often in the cabazitaxel arm, particularly haematological (68.2% vs. 47.3%, p < 0.0002) but also nonhaematological (57.4 vs. 39.8%, p < 0.0002) toxicity. In two post-marketing randomised phase III trials, cabazitaxel was shown not to be superior to docetaxel in the first-line setting; in the second-line setting in terms of OS, 20 mg/m^2 cabazitaxel was not inferior to 25 mg/m2, but less toxic. Therefore, the lower dose should be preferred [1335, 1336]. Cabazitaxel should preferably be given with prophylactic granulocyte colony-stimulating factor (G-CSF) and should be administered by physicians with expertise in handling neutropenia and sepsis [1337].

6.7.7.b Abiraterone acetate after docetaxel for mCRPC

Positive results of the large phase III trial (COU-AA-301) were reported after a median follow-up of 12.8 months [1338] and confirmed by the final analysis [1339]. A total of 1,195 patients with mCRPC were randomised 2:1 to AAP or placebo plus prednisone. All patients had progressive disease based on the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens). The primary endpoint was OS, with a planned HR of 0.8 in favour of AAP. After a median follow-up of 20.2 months, the median survival in the AAP group was 15.8 months compared to 11.2 months in the placebo arm (HR: 0.74, $p < 0.0001$). The benefit was observed in all subgroups, and all the secondary objectives were in favour of AAP (PSA, radiologic tissue response, time to PSA or objective progression). The incidence of the most common grade 3–4 AEs did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the AAP group, mainly grade 1–2 (fluid retention, oedema and hypokalaemia).

6.7.7.c Enzalutamide after docetaxel for mCRPC

The planned interim analysis of the AFFIRM study was published in 2012 [1340]. This trial randomised 1,199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. The patients had progressed after docetaxel treatment, according to the PCWG2 criteria. Corticosteroids were not mandatory, but could be prescribed, and were received by about 30% of the patients. The primary endpoint was OS, with an expected HR benefit of 0.76 in favour of enzalutamide. After a median follow-up of 14.4 months, the median survival in the enzalutamide group was 18.4 months compared to 13.6 months in the placebo arm (HR: 0.63, $p < 0.001$). This led to the recommendation to halt and unblind the study. The benefit was observed irrespective of age, baseline pain intensity, and type of progression. In the final analysis with longer follow-up the OS results were confirmed despite crossover and extensive post-progression therapies [1194]. Enzalutamide was active also in patients with visceral metastases.

All the secondary objectives were in favour of enzalutamide (PSA, soft tissue response, QoL, time to PSA, or objective progression). No difference in terms of side effects was observed in the two groups, with a lower incidence of grade 3–4 AEs in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm.

6.7.7.d Radium-223 after docetaxel for mCRPC

The only bone-specific drug that is associated with a survival benefit is the α-emitter radium-223. In a large phase III trial (ALSYMPCA) 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomised to six injections of 50 kBq/kg radium-223 or placebo plus SOC. The primary endpoint was OS. Radium-223 significantly improved median OS by 3.6 months (HR: 0.70, $p < 0.001$) and was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL [1341]. The associated toxicity was mild and, apart from slightly more haematologic toxicity and diarrhoea with radium-223, did not differ significantly from that in the placebo arm [1341]. Radium-223 was effective and safe whether or not patients were docetaxel pretreated [1342]. Due to safety concerns following ARPI combination treatment use of radium-223 was restricted by EMA to after docetaxel and at least one AR targeted agent [1343]. In particular, the use of radium-223 in combination with AAP showed significant safety risks related to fractures and more deaths. This was most striking in patients without the concurrent use of bone health agents [1344] so that radium-223 should always be used together with bone health agents (see Section 6.7.11.b).

6.7.7.e Rucaparib after ARPI

The phase III TRITON-3 trial randomised 405 mCRPC patients [1299]. Patients were selected for a *BRCA1, BRCA2,* or ATM alteration and disease progression after treatment with an ARPI for mCRPC. Treatment was as follows: rucaparib 600 mg twice daily or a physician's choice control, either second line docetaxel or the ARPI which had not been given previously. The first endpoint rPFS in the intention-to-treat group was significantly better with rucaparib (median 10.2 months and 6.4 months, respectively; HR 0.61; 95% CI, 0.47 to 0.80; $p < 0.001$). The small ATM subgroup did not derive a benefit. An interim analysis revealed OS to be immature. The study design allowed for cross-over and 60% of patients received a PARP inhibitor at progression (47% rucaparib). With regards to the control arms, the median rPFS was longer with rucaparib than with docetaxel (11.2 months vs. 8.3 months; hazard ratio, 0.53; 95% CI, 0.37 to 0.77) and it was also longer than with an ARPI (11.2 months vs. 4.5 months; hazard ratio, 0.38; 95% CI, 0.25 to 0.58). The most frequent adverse events with rucaparib were fatigue, nausea and anaemia, including 24% Grade ≥ 3 anaemia and 29% of patients on rucaparib required at least one blood transfusion [1345]. Rucaparib has been approved by the FDA.

6.7.7.f Olaparib after ARPI

See Section 6.7.8.c, 'PARP inhibitors for mCRPC'.

6.7.7.g ^{177}Lu-PSMA-617 after ARPI

Primary and updated analyses of rPFS for the phase III, multicentre RCT, PSMAfore, investigating taxane-naive patients with PSMA-positive mCRPC who had progressed on ARPI, have been published. Patients were 1:1 randomised between open-label, intravenous ^{177}Lu-PSMA-617 (7.4GBq intravenously, every six weeks, for up to six cycles) and a change of ARPI. A total of 468 patients met all eligibility criteria and were randomly assigned to receive ^{177}Lu-PSMA-617 (234 [50%] patients) or ARPI change (234 [50%]). Crossover was allowed. In the updated analysis at time of the third data cut-off (median time from randomisation to third data cut-off 24.11 months [IQR 20.24–27.40]), median rPFS was 11.60 months (95% CI: 9.30–14.19) in the ^{177}Lu-PSMA-617 group vs. 5.59 months (4.21–5.95) in the ARPI change group (HR 0.49 [95% CI: 0.39–0.61]) [1346].

In the final analysis the key secondary endpoint of OS did not show a statistically significant difference between the ^{177}Lu-PSMA-617 and the ARPI arms. In total 141/234 participants (60.3%) randomised to ARPI change crossed over to receive ^{177}Lu-PSMA-617. The median OS was 24.48 months with ^{177}Lu-PSMA-617 versus 23.13 with ARPI change (HR 0.91; 95% CI 0.72–1.14; p = 0.20); For ^{177}Lu-PSMA-617 versus ARPI change, exposure-adjusted incidences of grade ≥ 3 and serious treatment-emergent adverse events were 60.8 versus 85.1 and 32.5 versus 49.9 per 100 patient-treatment years, respectively [1347]. Dry mouth occurred in 135/227 participants (59.5%; 2/227 grade ≥ 3) and anaemia in 62/227 (27.3%; 14/227 grade ≥ 3) in the ^{177}Lu-PSMA-617 arm.

6.7.8 Treatment after docetaxel and one line of ARPI for mCRPC

6.7.8.a General considerations

For men progressing quickly on AR targeted therapy (< twelve months) it is now clear that cabazitaxel is the treatment supported by the best data. The CARD trial, an open label randomised phase III trial, evaluated cabazitaxel after docetaxel and one line of ARPI (either AAP or enzalutamide) [1293]. It included patients progressing in less than twelve months on previous abiraterone or enzalutamide for mCRPC. Cabazitaxel more than doubled rPFS vs. another ARPI and reduced the risk of death by 36% vs. ARPI. The rPFS with cabazitaxel remained superior regardless of the ARPI sequence and if docetaxel was given before, or after, the first ARPI.

The choice of further treatment after docetaxel and one line of HT for mCRPC is open for patients who have a > 12 months response to first-line abiraterone or enzalutamide for mCRPC [1315]. Either second-line chemotherapy (cabazitaxel), radium-223 (if bone-only metastases), ^{177}Lu–PSMA-617 radioligand therapy [1348, 1349] and PARP inhibitors (if BRCA mutation) are valuable options.

Men previously treated with at least one ARPI or both an ARPI and docetaxel and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA-repair genes showed an 88% response rate to olaparib [1350] and in another confirmatory trial a composite response of 54.3% (95% CI: 39.0–69.1) in the 400 mg cohort and in 18 of 46 (39.1%; 25.1–54.6) evaluable patients in the 300 mg cohort [1351]. In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use [1352, 1353] and there is evidence of cross-resistance between enzalutamide and abiraterone [1354, 1355]. This cross resistance with abiraterone should also be extrapolated to apalutamide and darolutamide. Also, the sequential use of the lutamides (apalutamide, darolutamide, enzalutamide) is not recommended as the mode of action is very similar.

6.7.8.b Radiopharmaceuticals

6.7.8.b.1 Introduction

Historically, several radiopharmaceuticals including Phosphorous-32, Strontium-89, Yttrium-90, Samarium-153, and Rhenium-186 were developed for the treatment of bone pain secondary to metastases from PCa [1356]. They proved effective in a palliation setting, by relieving pain and improving QoL, especially in the setting of diffuse bone metastases. However, they never gained widespread adoption. The first radioisotope to demonstrate a survival benefit was Radium-223 (see Section 6.7.7.d).

6.7.8.b.2 PSMA-based therapy

The increasing use of radiolabelled PSMA hybrid imaging as a diagnostic tracer and the realisation that this allowed identification of a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope with a therapeutic isotope which accumulates where the tumour is demonstrated (theranostics) [1357]. Therefore, after identification of the target, usually with diagnostic PSMA PET tracers, therapeutic radiopharmaceuticals labelled with β (Lutetium-177 or yttrium-90) or α (Actinium-225)-emitting isotopes could be used to treat metastatic PCa.

The PSMA therapeutic radiopharmaceutical supported by the most robust data is ^{177}Lu-PSMA-617. The first patient was treated in 2014 and early clinical studies evaluating the safety and efficacy of ^{177}Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already progressed on multiple therapies [1358]. The early data were based on single-centre experience [1359]. Data from uncontrolled prospective phase II trials reported high response rates with low toxic effects [1360, 1361]. Positive results are also coming from a randomised phase II trial (TheraP) [1362].

In TheraP patients for whom cabazitaxel was considered the next appropriate standard treatment after docetaxel and who were highly selected by ^{68}Ga-PSMA-11 and ^{18}FDG PET-CT scans, were randomised to receive ^{177}Lu-PSMA-617 (6.0–8.5 GBq intravenously, every 6 weeks, for up to 6 cycles) or cabazitaxel (20 mg/m^2 for up to ten cycles). The primary endpoint was a reduction of at least 50% in PSA. The first endpoint was met (66% vs. 37% for ^{177}Lu–PSMA-617 vs. cabazitaxel, respectively, by intention to treat; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016) [1362]. Secondary outcomes of the TheraP trial, including survival after a median follow-up of 35.7 months (IQR 31.1 to 39.2) showed that 77 (78%) participants had died in the ^{177}Lu-PSMA-617 group and 70 (69%) participants in the cabazitaxel group. Overall survival was similar between randomly assigned patients in the two groups (19.1 vs. 19.6 months; difference -0.5, 95% CI: -3.7 to 2.7]; p = 0.77) [1363, 1364].

An open-label phase III trial (VISION) compared ^{177}Lutetium Vipivotid tetraxetan (^{177}Lu-PSMA-617 radioligand therapy) with protocol-permitted SOC (i.e., excluded chemotherapy, immunotherapy, radium-223 and investigational drugs) in mCRPC patients, with PSMA expressing metastases on PET/CT, previously treated with at least one ARPI and one (around 53%) or two taxanes. Imaging-based PFS and OS were the alternate primary endpoints. More than 800 patients were randomised. ^{177}Lu-PSMA-617 plus SOC significantly prolonged both imaging-based PFS and OS, as compared with SOC alone (see Table 6.6.3). Grade 3 or above AEs were higher with ^{177}Lu-PSMA-617 than without (52.7% vs. 38.0%), but QoL was not adversely affected. ^{177}Lu–PSMA-617 has shown to be an additional treatment option in this mCRPC population [1365]. In a post hoc analysis of the phase III VISION trial the magnitude of PSA decline was associated with improvement in clinical and patient-reported outcomes in patients with mCRPC receiving ^{177}Lu-PSMA-617 plus standard of care in VISION [1366].

A systematic review and updated meta-analysis, investigated the proportion of patients with any or more than 50% PSA decrease, and OS. The review, including 69 articles and a total of 4,157 patients, showed that patients treated with ^{177}Lu–PSMA 617 had a significantly higher response to therapy compared to controls, based on ≥ 50% PSA decrease (OR = 5.33, 95% CI: 1.24–22.90, p < 0.05). Meta-analysis revealed an OS of 0.26 according to pooled HRs for any PSA decline, which was significant after ^{177}Lu–PSMA-617 therapy (95% CI: 0.18–0.37, p < 0.00001) and an OS of 0.52 for ≥ 50% PSA decrease, also significant after radioligand (RLT) (95% CI: 0.40–0.67, p < 0.00001) [1367].

A multicenter retrospective study on 124 mCRPC patients treated with PSMA radionuclide therapy showed that PSMA PET/CT by Response Evaluation Criteria in Prostate-Specific Membrane Antigen Imaging (RECIP) 1.0 after two cycles of ^{177}Lu–PSMA-617 is prognostic for PSA-PFS, indicating that PSMA PET/CT by RECIP 1.0 may be used in earlier stages of PCa to evaluate drug efficacy and to predict PFS [1368].

^{177}Lu-PSMA-617 can measure tumour sites after each therapy by taking whole body 3D images at different timepoints post-injection, using a small radiation wave from the treatment itself [1369]. This is called a Single Photon Emission Computed Tomography (SPECT) scan. SPECT detects gamma emissions from ^{177}Lu, allowing visualisation of radioligand distribution within the body and confirming tumour targeting. There is growing evidence that SPECT can be used as an imaging response biomarker [1370].

The earlier use of ^{177}Lu-PSMA-617 was studied in patients progressing on the first ARPI for mCRPC (PSMAfore) [1346], see Section 6.7.7.g.

The reintroduction of ^{177}Lu-PSMA therapy has been proposed in relapsed mCRPC patients who initially responded to PSMA-radionuclide therapy experiencing partial remission, but relapsed into progression after a certain period of remission. Several authors have investigated the feasibility of this approach in terms of safety and efficacy. In a retrospective analysis forty seven patients with mCRPC who had biochemical response to initial [^{177}Lu]Lu-PSMA-617 RLT followed by disease progression received at least one (up to three) series of [^{177}Lu]Lu-PSMA-617 RLT rechallenge. After one series of RLT rechallenge, a PSA decline of at least 50% was achieved in 57%. The median PFS of all patients was 8.7 months and the median OS was 22.7 months [1371].

There is an increasing interest in PSMA-targeted alpha therapy (^{225}Ac-PSMA) due to the ability to deliver potent higher local radiation more selectively to cancer cells than PSMA-targeted beta therapy, while minimising unwanted damage to the surrounding normal tissues. Additionally, the intensive radiation to cancer cells results in more effective DNA strand breakage and reduces the development of treatment resistance. A meta-analysis, including nine studies with 263 patients, investigated the therapeutic effects of ^{225}Ac-PSMA RLT in patients with metastatic CRPC, pretreated with chemotherapy, ^{177}Lu-PSMA and/or radium-223. The pooled proportions of patients with more than 50% PSA decline and any PSA decline were 60.99% (95% CI: 54.92%– 66.83%) and 83.57% (95% CI: 78.62%–87.77%), respectively. The estimated mean PFS and mean OS were 9.15 months (95% CI: 6.69–11.03 months) and 11.77 months (95% CI: 9.51–13.49 months), respectively. These findings suggest that ^{225}Ac-PSMA RLT may be an effective treatment option for patients with mCRPC [1372]. Despite the encouraging therapeutic response and survival of patients who received ^{225}Ac-PSMA RLT, major AEs such as xerostomia and severe haematotoxicity must be considered possible reasons for dose reduction or discontinuation of the therapy.

A retrospective, multicentre international study, WARMTH Act, pooled data of 488 men with mCRPC, who received one or more cycles of 8 MBq ^{225}Ac-PSMA RLT, across 7 international centres [1373]. Patients were heavily pretreated (docetaxel 66%, cabazitaxel 21%, abiraterone 39%, enzalutamide 39%, ^{177}Lu-PSMA RLT 32% and 223Ra dichloride 4%). The median follow-up was 9.0 months. The median OS was 15.5 months (95% CI: 13.4–18.3) and median PFS was 7.9 months (CI: 6.8–8.9). In 347 (71%) out of 488 patients, information regarding treatment-induced xerostomia was available, with 236 (68%) of the 347 patients reporting xerostomia after the first cycle of ^{225}Ac-PSMA RLT. Grade 3 or higher anaemia occurred in 64 (13%) of 488 patients, leukopenia in 19 (4%), thrombocytopenia in 32 (7%), and renal toxicity in 22 (5%). No serious AEs or treatment-related deaths were recorded. This study supports previous data showing that ^{225}Ac-PSMA RLT has a substantial antitumour effect, being a viable therapy option in heavily pretreated mCRPC patients, including patients after ^{177}Lu-PSMA RLT. Comparable results, with a median OS of 15 months (95% CI: 10-19; median follow-up was 22 months), were reported in a series of patients with mCRPC treated with ^{225}Ac-PSMA (100-150 kBq/kg at least two cycles, at eight weeks), after becoming resistant to all previous anticancer agents [1374]. The side effect profile remains to be elucidated. So far, ^{225}Ac-PSMA RLT for mCRPC has not been approved.

Combined therapies, including ^{177}Lu-PSMA radionuclide therapy, in mCRPC have moved into the focus of clinical research. In an open-label, multicentre, randomised, phase II trial, EnzaP, participants not previously treated with docetaxel or an ARPI for mCRPC were randomly assigned (1:1) to oral enzalutamide 160 mg daily alone or with adaptive-dosed (two or four doses) 7.5 GBq ^{177}Lu-PSMA-617 intravenous, every 6–8 weeks, based on a 12-week interim PSMA PET/CT [1375]. The primary endpoint was PSA PFS. Overall, 83 men were assigned to the enzalutamide plus ^{177}Lu-PSMA-RLT group, and 79 were assigned to enzalutamide alone. Median PSA PFS was 13.0 months (95% CI: 11.0–17.0) in the enzalutamide plus RLT group and 7.8 months (95% CI: 4·3–11·0) in the enzalutamide group (HR 0.43, 95% CI: 0.29–0.63, p < 0·0001). The most common AEs were fatigue (75%), nausea (47%), and dry mouth (40%) in the enzalutamide plus RLT and fatigue (70%), nausea (27%], and constipation (23%) in the enzalutamide alone group [1375]. The actual benefit of the combined use, in particular, in patients pretreated by one or two ARPIs is still to be proven in larger prospective controlled trials, and a firm recommendation would be premature.

6.7.8.c PARP inhibitors for mCRPC

So far, two PARP inhibitors as monotherapy, olaparib and rucaparib, are licenced by the FDA (EMA only approved olaparib) and several other PARP inhibitors are under investigation or were approved only in combination with an ARPI (see Section 6.7.6.e).

A randomised phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARPI in mCRPC with alterations in ≥ 1 of any qualifying gene with a role in HRR and progression on an ARPI. Most patients were heavily pretreated with 1–2 chemotherapies and up to 2 ARPIs [341, 1197]. Radiographic PFS by blinded independent central review in the *BRCA1/2* or *ATM* mutated population (Cohort A) was the first endpoint and significantly favoured olaparib (HR: 0.49, 95% CI: 0.38–0.63). The final results for OS demonstrated a significant improvement among men with *BRCA1/2* or *ATM* mutations (Cohort A) (p = 0.0175; HR: 0.69, 95% CI: 0.50– 0.97). This was not significant in men with any (other) HRR alteration (Cohort B) (HR: 0.96, 95% CI: 0.63–1.49). Of note, 66% (n = 86 of 131) patients in the physician's choice of enzalutamide/abiraterone-arm who progressed, crossed over to olaparib.

The most common AEs were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib vs. enzalutamide/abiraterone. Among patients receiving olaparib 16.4% discontinued treatment secondary to an AEs, compared to 8.5% of patients receiving enzalutamide/abiraterone. Of patients receiving olaparib, 4.3% of patients had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukaemia. This was the first trial to show a benefit for genetic testing and precision medicine in mCRPC.

The FDA approved olaparib for patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with *BRCA1* and *BRCA2* alterations [1376]. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food.

Rucaparib has been approved by the FDA for patients with deleterious *BRCA* mutations (germline and/or somatic) who have been treated with ARPI and a taxane-based chemotherapy [1377]. Approval was based on the results of the single-arm TRITON2 trial (NCT02952534). The confirmed ORR per independent radiology review in 62 patients with deleterious *BRCA* mutations was 43.5% (95% CI: 31–57) [1378]. Rucaparib second line after ARPI was studied in the TRITON 3 trial and is discussed in Section 6.7.7.e.

The combination of ARPI plus a PARP inhibitor in first-line mCRPC was studied in several RCT including AAP plus Olaparib [1198], AAP plus Niraparib [1202] and Enzalutamide plus Talazoparib [1205]. See Table 6.7.2.

6.7.8.d Sequencing treatment

6.7.8.d.1 ARPI -> ARPI (chemotherapy-naive mCRPC patients)

The use of sequential ARPIs in mCRPC showed limited benefit in retrospective series as well as in one prospective trial [1379-1386]. In patients who had a short response to the first ARPI for mCRPC (< twelve months), this sequence should be avoided because of known cross resistance and the availability of chemotherapy and PARP inhibitors (if a relevant mutation is present). In the control arm of the contemporary PSMAfore trial, the ARPI-switch showed an rPFS of 5.59 months (4.21–5.95) [1346]. Based on an rPFS benefit Lutetium Lu 177 vipivotide tetraxetan may be approved in Europe, in this setting, soon and would be preferred to an ARPI switch. An FDA approval is already in place and Lutetium Lu 177 vipivotide tetraxetan's indication now includes PSMA-positive mCRPC post-AR inhibitor therapy where delaying taxane-based chemotherapy is appropriate [1387].

In highly selected patients treated for more than 24 weeks with AAP, the sequence with enzalutamide showed some activity with a median rPFS of 8.1 months (95% CI: 6.1–8.3) and an unconfirmed PSA response rate of 27% [1295]. In case the patient is unfit for chemotherapy and a PARP inhibitor, best supportive care should be considered in case no other appropriate treatment option is available (clinical trial or immunotherapy if MSI-high). An ARPI-ARPI sequence should never be the preferred option but might be considered in such patients if the PS still allows for active treatment and the potential side effects seem manageable.

First prospective cross-over data on an ARPI-ARPI sequence [1379] and a SR and meta-analysis suggest that for the endpoints PFS and PSA PFS, but not for OS, abiraterone followed by enzalutamide is the preferred choice [1388].

6.7.8.d.2 ARPI -> PARP inhibitor

This sequence in patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC is supported by data from the randomised phase III PROfound trial studying olaparib [1197] and TRITON 3 studying rucaparib [1299]. A subgroup of patients in PROfound was pretreated with one or two ARPIs and no chemotherapy (35%).

The ARPI-PARP inhibitor sequence versus ARPI-ARPI or ARPI-docetaxel in patients with *BRCA 1/2* (and ATM) altered tumours was studied in TRITON-3 and showed a significant rPFS benefit in favour of the PARP inhibitor following the first ARPI. These data underscore the importance of early genomic testing in mCRPC patients and prioritisation of PARP inhibitor treatment very early on in patients with *BRCA* or *HRR* mutations. This message is also supported by the AMPLITUDE study, showing a rPFS benefit with the addition of niraparib to abiraterone in patients with mHSPC and HRR mutations (see also chapter 6.7.7.e) [1259].

6.7.8.d.3 *Docetaxel for mHSPC -> docetaxel rechallenge*

There is limited evidence for second- or third-line use of docetaxel after treatment with docetaxel for mHSPC. Docetaxel seems to be less active than ARPI at progression to mCRPC following docetaxel for mHSPC [1389].

6.7.8.d.4 *ARPI -> docetaxel or docetaxel -> ARPI followed by PARP inhibitor*

Both olaparib and rucaparib are active in biomarker-selected mCRPC patients after ARPI and docetaxel in either sequence [1197, 1377].

6.7.8.d.5 *ARPI before or after docetaxel*

There is level 1 evidence for both sequences (Table 6.7.3).

6.7.8.d.6 *ARPI -> docetaxel -> cabazitaxel or docetaxel -> ARPI -> cabazitaxel*

Both third-line treatment sequences are supported by level 1 evidence. Of note, there is high-level evidence favouring cabazitaxel vs. a second ARPI after docetaxel and one ARPI in particular in patients progressing ≤ 12 months on a prior ARPI. CARD is the first prospective randomised phase III trial addressing this question (Table 6.7.3) [1293].

6.7.8.e Platinum chemotherapy

Cisplatin or carboplatin as monotherapy or combinations have shown limited activity in unselected patients in the pre-docetaxel era [1390]. The combination of cabazitaxel and carboplatin was evaluated in pretreated mCRPC patients in a randomised phase I/II trial. The combination improved the median PFS from 4.5 months (95% CI: 3.5–5.7) to 7.3 months (95% CI: 5.5–8.2; HR: 0.69, 95% CI: 0.50–0.95, p = 0.018) and the combination was well tolerated [1391]. On a histopathological and molecular level, there is preliminary evidence that platinum adds efficacy in patients with aggressive variant PCa molecular signatures including *TP53, RB1,* and *PTEN* [1392].

Patients with mCRPC and alterations in DDR genes are more sensitive to platinum chemotherapy than unselected patients [1393], also after progression on PARP inhibitors. Interestingly, in contemporary retrospective series, unselected patients as well as patients without DDR gene alterations also showed a 50% PSA decline when treated with platinum in up to 36% of patients [1360].

In a MA of 23 studies with 901 *BRCA*-positive mCRPC patients the PSA 50 response rates for PARPi and platinum were 69% (CI: 53–82%), and 74% (CI: 49–90%), respectively. Analyses of OS data showed no difference between PARPi and platinum treatments (HR: 0.86; CI: 0.49-1.52; p = 0.6) [1394]. This analysis supports the use of platinum in patients with *BRCA* alterations in particular after progression on PARPi or if PARPi are unavailable or suspended due to AEs.

In view of the excellent tolerability of e.g. carboplatin monotherapy, platinum could be offered to patients with far advanced mCRPC harbouring DDR gene aberrations after having progressed on standard treatment options. Prospective controlled trials are ongoing.

6.7.9 *Treatment emergent neuroendocrine PCa and neuroendocrine subtype*

Neuroendocrine prostate carcinoma (NEPC) is an aggressive variant of PCa, exhibiting characteristics comparable to small cell lung cancer (SCLC). Clinically, NEPC is differentiated based on whether the variant is already dominant at the time of diagnosis or develops only after prior ADT and/or androgen receptor pathway inhibitors (ARPI), distinguishing between *de novo* or primary NEPC and the treatment-related or so-called treatment-emergent NEPC [1395].

Treatment-related neuroendocrine prostate carcinoma (t-NEPC) is the only neuroendocrine histological subtype, primarily associated with prostate tumours, that is included in the 2022 WHO classification. The incidence of t-NEPC is rising and is estimated to account for between 15 and 20% of all CRPC cases [1396]. In contrast to primary neuroendocrine neoplasms (NENs), t-NEPC arises from adenocarcinomas or from the castration-resistant variant of PCa following potent anti-hormonal therapy through a process called transdifferentiation.

Clinically, it is important to acknowledge that in addition to AR-dependent castration-resistant adenocarcinomas, there is a subgroup of patients with AR-independent tumour biology. The variants of androgen-indifferent PCa (AIPC) include aggressive variant PCa (AVPC), NEPC, and double-negative PCa (DNPC) [1397]. Aggressive variant PCa has been defined as CRPC with at least one of the following characteristics [1392]:

1. Histological evidence of small-cell neuroendocrine PCa.
2. Exclusively visceral metastases.
3. Predominantly lytic bone metastases.
4. Extensive lymphadenopathy or large tumour mass in the prostate/pelvis.
5. Low PSA level at initial diagnosis plus high tumour volume in the bones.
6. Neuroendocrine markers in histology or serum at initial diagnosis or during disease progression plus one of the following: elevated serum lactate dehydrogenase, malignant hypercalcemia, and/or elevated carcinoembryonic antigen (CEA) in the absence of other features.
7. Short interval (≤ 6 months) between initiation of hormone therapy and androgen-independent disease progression, with or without neuroendocrine markers,

A small subgroup of AVPC tumours express neither AR nor NE markers and are therefore referred to as Double-negative PCa [1398].

If the transformation into t-NEPC or a pure NEPC is suspected, a tissue biopsy is required to confirm the diagnosis (e.g. new liver metastases and low PSA or signs of AVPC characteristics).

There is no clearly defined, evidence-based standard of care established through comparative data for AVPC. Treatment recommendations are largely guided by therapeutic protocols used for SCLC. It has been suggested to treat locally advanced or metastatic NEPC with a platinum-etoposide chemotherapy regimen with or without an immune checkpoint inhibitor, whilst AR positive PCa with only minor amounts of neuroendocrine de-differentiation should be managed with either docetaxel monotherapy or rather taxane in combination with a platinum agent [1399]. However, no recommendations based on randomised phase III trials can be given.

Table 6.7.1: Phase III randomised controlled trials – nmCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ARAMIS 2019, 2020 [1305, 1400]	ADT + darolutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2ng/mL PSA-DT ≤ 10 mo.	**59% reduction of distant progression or death** **Median MFS: darolutamide 40.4 vs. placebo 18.4 mo.; 31% reduction in risk of death** HR = 0.69 (95% CI: 0.53–0.88) p = 0.003
PROSPER 2018, 2020 [1303, 1401]	ADT + enzalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2ng/mL PSA-DT ≤ 10 mo.	**71% reduction of distant progression or death** **Median MFS: enzalutamide 36.6 vs. placebo 14.7 months; 27% reduction in risk of death** HR = 0.73 (95% CI: 0.61–0.89) p = 0.001
SPARTAN 2018, 2021 [1304, 1402]	ADT + apalutamide	ADT + placebo	nmCRPC; baseline PSA ≥ 2ng/mL PSA-DT ≤ 10 mo.	**72% reduction of distant progression or death** **Median MFS: apalutamide 40.5 vs. placebo 16.2 months;** **22% reduction in risk of death** HR = 0.78 (95% CI: 0.64–0.96) p = 0.0161

ADT = androgen-deprivation therapy; CI = confidence interval; HR = hazard ratio; MFS = metastasis-free survival; mo. = months; nmCRPC = nonmetastatic castrate-resistant prostate cancer; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time.

Table 6.7.2: Phase III randomised controlled trials - first-line treatment of mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
DOCETAXEL				
SWOG 99-16 2004 [1403]	docetaxel/EMP, every 3 weeks, 60 mg/m^2, EMP 3 x 280 mg/day	mitoxantrone, every 3 weeks, 12 mg/m^2 prednisone 5 mg BID		**OS: 17.52 vs. 15.6 mo.** (p = 0.02, HR: 0.80; 95% CI: 0.67–0.97) **PFS: 6.3 vs. 3.2 mo.** (p < 0.001)
TAX 327 2004, 2008 [1316, 1317]	docetaxel, every 3 weeks, 75 mg/m^2 prednisone 5 mg BID or docetaxel, weekly, 30 mg/m^2 prednisone 5 mg BID	mitoxantrone, every 3 weeks, 12 mg/m^2, prednisone 5 mg BID		**OS: 19.2 for 3-weekly vs. 17.8 mo. 4-weekly and 16.3 in the control group.** (p = 0.004, HR: 0.79, 95% CI: 0.67–0.93)
ABIRATERONE				
COU-AA-302 2013, 2014, 2015 [1308, 1309, 1404]	abiraterone + prednisone	placebo + prednisone	No previous docetaxel ECOG 0–1 PSA or radiographic progression No or mild symptoms No visceral metastases	**OS: 34.7 vs. 30.3 mo.** (HR: 0.81, p = 0.0033) **FU: 49.2 mo. rPFS: 16.5 vs. 8.3 mo.** (p < 0.0001)
ENZALUTAMIDE				
PREVAIL 2014 [1311]	enzalutamide	placebo	No previous docetaxel ECOG 0–1 PSA or radiographic progression No or mild symptoms 10% had visceral mets	**OS: 32.4 vs. 30.2 mo.** (p < 0.001). FU: 22 mo. (p < 0.001 HR: 0.71, 95% CI: 0.60–0.84) **rPFS: 20.0 mo. vs. 5.4 mo.** HR: 0.186 (95% CI: 0.15–0.23) p < 0.0001)
SIPULEUCEL-T				
IMPACT 2010 [1405]	sipuleucel-T	placebo	Some with previous docetaxel ECOG 0–1 Asymptomatic or minimally symptomatic ECOG 0–1 No visceral met. No corticosteroids	**OS: 25.8 vs. 21.7 mo.** (p = 0.03 HR: 0.78, 95% CI: 0.61–0.98). **FU: 34.1 mo. PFS: 3.7 vs. 3.6 mo.** (no difference)
2006 [1406]	sipuleucel-T	placebo		**OS: 25.9 vs. 21.4 mo.** (p = 0.1) **FU: 36 mo. PFS: 11.7 vs. 10.0 wk.**
COMBINATIONS				
PROpel [1198, 1199]	olaparib (300mg BID) + abiraterone (1000 mg/d) + prednisone (5 mg BID)	placebo + abiraterone + prednisone	ECOG 0-1 regardless of HRRm (retrospective testing) prior taxane for mHSPC allowed	**ibPFS in ITT population: 24.8 vs. 16.6 mo.;** HR: 0.66; 95% CI: 0.54–0.81; (p = 0.001) ibPFS in BRCA+: HR 0.24; 95% CI: 0.12-0.45 **OS in ITT population: 42.1 vs. 38.9 mo.;** HR 0.81; 0.95% CI: 0.81, 0.67-1.0; (p= 0,054) OS in BRCA+: HR 0.30; 95% CI: 0.15-0.59

MAGNITUDE [1203, 1407]	niraparib 200 mg/d + abiraterone (1,000 mg/d plus prednisone 5 mg BID)	placebo + abiraterone (1,000 mg/d plus prednisone 5 mg BID)	ECOG 0-1 AAP ≤ 4mo allowed for mCRPC HRR-biomarker-positive cohort prior docetaxel for mHSPC allowed prior ARPI for mHSPC allowed prior ARPI for mCRPC allowed	**rPFS (central review) in HRR+: 16.5 vs. 13.7 mo.** HR = 0.73; 95% CI: 0.56-0.96; (p = 0.022) **rPFS (central review) in *BRCA* 1/2+:** rPFS 19.5 versus 10.9 months; HR= 0.55; 95% CI 0.39-0.78; (nominal p= 0.0007)
TALAPRO-2 [1205, 1296, 1325-1327]	talazoparib (0.5mg/d) + enzalutamide 160mg/d	enzalutamide + placebo	ECOG 0-1 All comers: HHR deficient and HRR non-deficient or unknown prior AAP or docetaxel allowed for mHSPC	**rPFS in ITT: NR (27.5-NR) vs. 21.9 mo.:** HR 0.63; 95% CI: 0.51-0.78 (p<0.0001); rPFS 33.1 vs. 19.5 mo.: HR 0·67; 95% CI 0·55–0·81; (p<0·0001); rPFS in BRCA+: HR 0.23; 95% CI: 0.10-0.53 p=0.0002 **Cohort 1:** OS in ITT (HRR- and HRR+): 45.8 vs. 37.0 mo. - HR 0.80; 95% CI: 0.66–0.96 (p=0.016); OS in HRR+: HR 0.55 95% CI 0.36–0.83; (p=0·0035) HRR- or unknown: HR 0.88; 0.71–1.08 (p=0.22) **Cohort 2:** ITT= HRR+ OS 45.1 vs. 31.1 mo.: HR 0.62; 95% CI 0.48–0.81; (two-sided p=0·0005); BRCA1/2+: OS NR vs. 28.5 mo.: HR 0.50; 95% CI 0.32–0.78; (p=0·0017); 4-yr., OS 53% vs 23%
PEACE-3 [1332]	enzalutamide 160 mg/d+ radium 223 (6 cycles)	enzalutamide	asymptomatic or mildly symptomatic ≥ 2 bone metastases, +/- additional lymph node metastases no visceral metastases prior docetaxel or abiraterone for mHSPC allowed bone protection mandatory (after amendment)	rPFS: 19.4 vs. 16.4 mo.: HR 0.69, 95% CI 0.54-0.87, (p=0.0009), OS: 42.3 vs. 35.0 mo.: HR 0.69, 95% CI 0.52-0.90, (p=0.0031)

AAP = abiraterone/prednisolone; ARPI = androgen receptor pathway inhibitors; BICR = blinded independent central review; BID = twice a day; BCRA+ = breast cancer gene mutation; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EMP = estramustine; FU = follow-up; HR = hazard ratio; HRRm = homologous recombination repair genes mutation; ib = imaging based; IHC = immunohistochemistry; LN = lymph node; mets. = metastases; mo. = months; ib (imaging based); (r)PFS = (radiographic) progression-free survival; PSA = prostate-specific antigen; OS = overall survival; IHC = immunohistochemistry.

Table 6.7.3: Phase II/III randomised controlled trials in second-line/third-line mCRPC

Study	Intervention	Comparison	Selection criteria	Main outcomes
ABIRATERONE				
COU-AA-301 2012 [1339]	abiraterone + prednisone HR	placebo + prednisone	Previous docetaxel ECOG 0–2 PSA or radiographic progression	**OS: 15.8 vs. 11.2 mo.** (p < 0.0001, HR: 0.74; 95% CI: 0.64–0.86; p < 0.0001). FU: 20.2 mo. **rPFS: 5.6 vs. 3.6 mo.**
COU-AA-301 2011 [1338]				**OS: 14.8 vs. 10.9 mo.** (p < 0.001 HR: 0.65; 95% CI: 0.54–0.77). FU: 12.8 mo. **rPFS: 5.6 vs. 3.6 mo.**
Radium-223				
ALSYMPCA 2013 [1341]	radium-223	placebo	Previous or no previous docetaxel ECOG 0–2 Two or more symptomatic bone metastases No visceral metastases	**OS: 14.9 vs. 11.3 mo.** (p = 0.002, HR: 0.61; 95% CI: 0.46–0.81). All secondary endpoints show a benefit over best SOC.
CABAZITAXEL				
TROPIC 2013 [1408]	cabazitaxel + prednisone	mitoxantrone + prednisone	Previous docetaxel ECOG 0–2	**OS: 318/378 vs. 346/377 events** (OR: 2.11; 95% CI: 1.33–3.33). FU: 25.5 mo. OS ≥ 2 yr. 27% vs. 16% PFS
TROPIC 2010 [1334]				**OS: 15.1 vs. 12.7 mo.** (p < 0.0001, HR: 0.70; 95% CI: 0.59–0.83). FU: 12.8 mo. **PFS: 2.8 vs. 1.4 mo.** (p < 0.0001, HR: 0.74, 95% CI: 0.64–0.86)
CARD 2019 [1293]	cabazitaxel (25 mg/m2 Q3W) + prednisone + G-CSF	ARPI: abiraterone + prednisone OR Enzalutamide	Previous docetaxel Progression ≤ 12 mo. on prior alternative ARPI (either before or after docetaxel)	**Med OS 13.6 vs. 11.0 mo.** (p = 0.008, HR: 0.64, 95% CI: 0.46–0.89). **rPFS 8.0 vs. 3.7 mo.** (p < 0.001, HR: 0.54, 95% CI: 0.40–0.73). FU: 9.2 mo.
ENZALUTAMIDE				
AFFIRM 2012 [1340]	enzalutamide	Placebo	Previous docetaxel ECOG 0–2	**OS: 18.4 vs. 13.6 mo.** (p < 0.001, HR: 0.63; 95% CI: 0.53–0.75). FU: 14.4 mo. **rPFS: 8.3 vs. 2.9 mo.** (HR: 0.40; 95% CI: 0.35–0.47, p < 0.0001).

PARP inhibitor				
PROfound 2020 [341, 1197, 1351]	olaparib	abiraterone + prednisolone or enzalutamide; cross-over allowed at progression	- Previous ARPI, alterations in HRR genes	**rPFS: 7.39 vs. 3.55 mo.** (p < 0.0001, HR: 0.34; 95% CI: 0.25–0.47), conf. ORR 33.3% vs. 2.3% (OR 20.86, 95% CI: 4.18–379.18). **OS: 19.1 mo vs. 14.7 mo** (in patients with BRCA1/2, ATM alterations) (p = 0.0175; HR 0.69; 95% CI: 0.5–0.97).
TRITON-3 [1299]	rucaparib (600 mg BID)	docetaxel or abiraterone acetate or enzalutamide	EOCG 0-1 Previous one ARPI *BRCA* 1/2 or ATM alteration	**rPFS: ITT 10.2 mo vs. 6.4 mo,** (HR 0.61; 95% CI, 0.47 to 0.80; p < 0.001 for both comparisons)
Radioligand therapy				
VISION 2021 [1365]	^{177}Lu-PSMA-617 SOC	SOC alone	Previous at least 1 ARPI and one or two taxane regimens; Mandatory: PSMA-positive gallium-68 (^{68}Ga)–labelled PSMA-PET scan	**Imaging-based PFS: 8.7 vs. 3.4 mo.** (p < 0.001; HR 0.40; 99.2% CI: 0.29–0.57) OS: **15.3 vs. 11.3 mo.** (p < 0.001; HR 0.62; 95% CI: 0.5–0.74)
TheraP 2021 [1362, 1363]	^{177}Lu-PSMA-617 (8.5 GBq i.v.q. 6-weekly, decreasing 0.5 GBq/cycle; up to 6 cycles)	^{177}Lu-PSMA-617 1:1 randomisation cabazitaxel (20 mg/m2 i.v.q. 3-weekly, up to 10 cycles)	Post docetaxel Suitable for cabazitaxel	**First endpoint PSA reduction of > 50%:** 66 vs. 37 PSA responses; 66% vs. 37% by ITT; difference 29% (95% CI: 16–42; p < 0.0001; and 66% vs. 44% by treatment received; difference 23% [9–37]; p = 0.0016). **Secondary endpoint OS:** 19.1 vs. 19.6 mo (^{177}Lu-PSMA vs. cabazitaxel). HR: 0.97, 95% CI: 0.7-1.4 (p = 0.99)
PSMAfore 2023 [1346, 1347]	^{177}Lu-PSMA-617 at a dosage of 7·4 GBq (200 mCi) ± 10%; 6 cycles	^{177}Lu-PSMA-617 1:1 randomisation to ARPI- change (abiraterone or enzalutamide)	One previous ARPI for mCRPC No previous taxane in CRPC or mHSPC	**First endpoint:** rPFS 3rd data cut-off : 11·60 mo (95% CI 9·30–14·19) vs 5·59 mo (4·21–5·95) (HR 0·49 [95% CI 0·39–0·61]) **OS:** 24.48 vs. 23.13 HR 0.91; 95% CI 0.72–1.14 (p = 0.20)

**Only studies reporting survival outcomes as primary endpoints have been included.*
ARPI = androgen receptor pathway inhibitor; CI = confidence interval; CRCP = castrate-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; GBq = gigabecquerel; G-CFS = granulocyte colony stimulating factor; HR = hazard ratio; HRR = homologous recombination repair; i.v.q. = intravenous quantity; Lu = lutetium; mHSPC = metastatic hormone-sensitive prostate cancer; mo. = months; OS = overall survival; OR = odds ratio; ORR = objective response rate; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; (r)PFS = (radiographic) progression-free survival; SOC = standard of care; yr. = years.

6.7.10 ***Monitoring of treatment***

Baseline examinations should include a medical history, clinical examination, as well as baseline blood tests (PSA, total testosterone level, full blood count, renal function, baseline liver function tests, alkaline phosphatase), bone scan and CT of chest, abdomen and pelvis [1409, 1410]. The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and most likely not as beneficial as for patients with BCR or hormone-naive disease. Flares, PSMA upregulation and discordant results compared with PSA response or progression on ARPI have been described [1411]. Prostate-specific antigen alone is not reliable enough [1412] for monitoring disease activity in advanced CRPC, since visceral metastases may develop in men without rising PSA [1413]. Instead, the PCWG2 recommends a combination of bone scintigraphy and CT scans, PSA measurements and clinical benefit in assessing men with CRPC [1290]. A majority of experts at the 2015 Advanced Prostate Cancer Consensus Conference (APCCC) suggested regular review and repeating blood profile every two to three months with bone scintigraphy and CT scans at least every six months, even in the absence of a clinical indication [1409]. This reflects that the agents with a proven OS benefit all have potential toxicity and considerable cost and patients with no objective benefit should have their treatment modified. The APCCC participants stressed that such treatments should not be stopped for PSA progression alone. Instead, at least two of the three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment. For trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions and introduced the concept of no longer 'clinically benefiting' to underscore the distinction between first evidence of progression and the clinical need to terminate or change treatment [1290]. These recommendations also seem valid for clinical practice outside trials.

6.7.11 ***When to change treatment***

The timing of treatment change for men with metastatic prostate cancer remains a matter of debate, although it is clearly advisable to start or change treatment immediately in men with symptomatic progressing metastatic disease. Any treatment change should preferably precede development of *de novo* symptoms or worsening of existing symptoms. Although, the number of effective treatments is increasing, head-to-head comparisons are still rare, as are prospective data assessing the sequencing of available agents. Therefore, it is not clear how to select the most appropriate 'second-line' treatment, particularly in patients without HRR alterations or other biomarkers. A positive example, however, is the CARD trial, which clearly established cabazitaxel as the better third-line treatment in docetaxel pretreated patients after one ARPI compared to the use of a second ARPI [1293].

The ECOG PS has been used to stratify patients. Generally, men with a PS of 0–1 are likely to tolerate treatments and those with a PS of > 2 are less likely to benefit. However, it is important that treatment decisions be individualised, particularly when symptoms related to disease progression are impacting on PS. In such cases, a trial of active life-prolonging agents to establish if a given treatment will improve the PS may be appropriate. Sequencing of treatment is discussed in the summary papers published following the 2019 and 2022 APCCC Conferences [1414, 1415].

6.7.12 ***Symptomatic management in metastatic castration-resistant prostate cancer***

Castration-resistant PCa is usually a debilitating disease often affecting the elderly male. A multidisciplinary approach is required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers [1414, 1416]. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression.

6.7.12.a Common complications due to bone metastases

Most patients with CRPC have painful bone metastases. External beam RT is highly effective, even as a single fraction [1417, 1418]. A single infusion of a third-generation bisphosphonate could be considered when RT is not available [1419]. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture whatever its origin, clearly improving both pain and QoL [1420]. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases [1421, 1422]. Impending spinal cord compression is an emergency. It must be recognised early, and patients should be educated to recognise the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery or orthopaedic surgeon consultation should be planned to discuss a possible decompression, followed by EBRT [1423]. Otherwise, EBRT with, or without, systemic therapy, is the treatment of choice.

6.7.12.b Preventing skeletal-related events

6.7.12.b.1 Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anticancer treatments, with the exception of docetaxel, were available. Six hundred and forty-three patients who had CRPC with bone metastases were randomised to receive zoledronic acid 4 or 8mg every three weeks for fifteen consecutive months, or placebo [1424]. The 8mg dose was poorly tolerated and reduced to 4mg but did not show a significant benefit. However, at fifteen and 24 months of follow-up, patients treated with 4mg zoledronic acid had fewer SREs compared to the placebo group (44 vs. 33%, p = 0.021), and in particular fewer pathological fractures (13.1 vs. 22.1%, p = 0.015). Moreover, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates.

6.7.12.b.2 RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor κ-B ligand), a key mediator of osteoclast formation, function and survival. In M0 CRPC, denosumab has been associated with increased bone-MFS compared to placebo (median benefit: 4.2 months, HR: 0.85, p = 0.028) [1417]. This benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively) and neither the FDA, nor the EMA have approved denosumab for this indication [1425].

The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with mCRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 versus 17.1 months, respectively (HR: 0.82, p = 0.008). Both urinary N-telopeptide and bone-specific alkaline phosphatase were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (p < 0.0001 for both). However, these findings were not associated with any survival benefit and, in a post-hoc re-evaluation of endpoints, denosumab showed identical results when comparing SREs and symptomatic skeletal events [1426].

The potential toxicity (e.g. osteonecrosis of the jaw, hypocalcaemia) of these drugs must always be kept in mind (5–8.2% in M0 CRPC and mCRPC, respectively) [1427, 1428]. Patients should have a dental examination before starting therapy, as the risk of jaw necrosis is increased by several risk factors including a history of trauma, dental surgery or dental infection [1429]. In addition, the risk for osteonecrosis of the jaw increased numerically with the duration of use in a pivotal trial [1430] (one year versus two years with denosumab), but this was not statistically significant when compared to zoledronic acid [1425]. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab and zoledronic acid. Hypocalcaemia must be avoided by adequate intake of calcium and vitamin D before initiating therapy [1431]. Hypocalcaemia should be identified and prevented during treatment with bone protective agents (risk of severe hypocalcaemia is 8% and 5% for denosumab and zoledronic acid, respectively) [1428]. Serum calcium should be measured in patients starting therapy and monitored during treatment, especially during the first weeks and in patients with risk factors for hypocalcaemia or on other medication affecting serum calcium. Daily calcium (> 500 mg) and vitamin D (> 400 IU equivalent) are recommended in all patients, except in case of hypercalcaemia [1428, 1432, 1433].

6.7.13 Summary of evidence and recommendations for life-prolonging treatments of castrate-resistant disease

Summary of evidence	LE
Treatment for mCRPC will be influenced by which treatments patients have already been exposed to.	4

Recommendations	Strength rating
Ensure that testosterone levels are confirmed to be < 50ng/dL before diagnosing castrate-resistant PCa (CRPC).	Strong
Counsel, manage and treat patients with metastatic CRPC (mCRPC) in a multidisciplinary team.	Strong
Treat patients with mCRPC with life-prolonging agents.	Strong
Offer mCRPC patients somatic and/or germline molecular testing, as well as testing for mismatch repair deficiencies or microsatellite instability, if not done previously.	Strong

6.7.14 *Recommendations for systemic treatments of castrate-resistant disease*

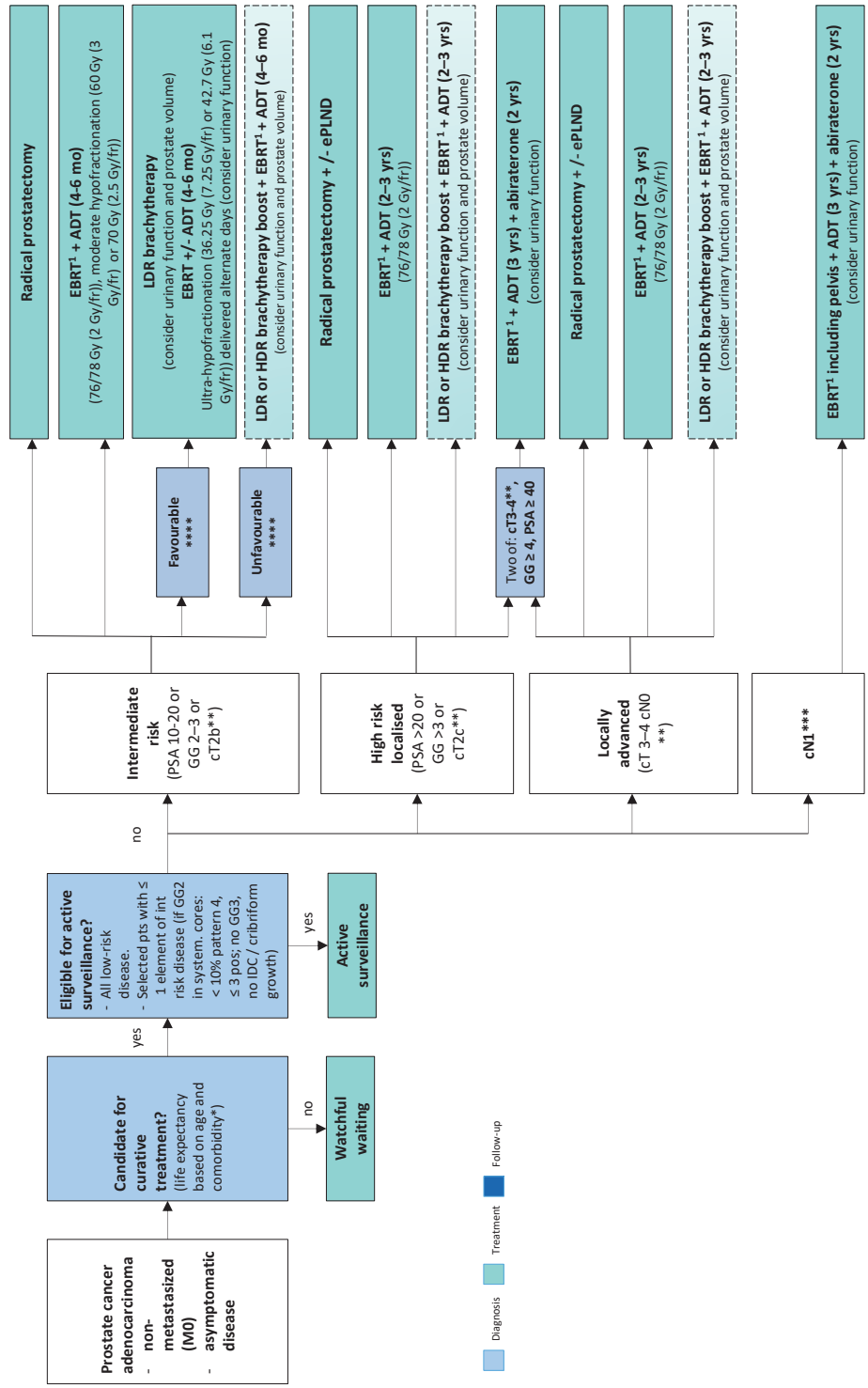
Summary statement for mCRPC first line combination therapy:
The combination of ARPI plus PARP inhibitors showed a significant rPFS benefit in RCTs for unselected patients. The OS benefit seen with enzalutamide plus talazoparib in the ITT population seems to be driven by the HRR-mutated group. The side effects of PARP inhibitors add substantial toxicity to ARPI monotherapy. Therefore, only a weak recommendation is given for the enzalutamide/talazoparib combination in patients without *HRR* or *BRCA 1/2* mutations.

Recommendations	Strength rating
Base the choice of treatment on the performance status (PS), symptoms, comorbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, ^{177}lutetium-PSMA-617-radioligand therapy, radium-223, sipuleucel-T and, for patients with DNA homologous recombination repair [*HRR*] alterations, olaparib, olaparib/abiraterone, niraparib/abiraterone, rucaparib, and talazoparib/enzalutamide).	Strong
Avoid sequencing of androgen receptor-targeted agents.	Weak
Offer chemotherapy to patients previously treated with an androgen receptor pathway inhibitor (ARPI).	Strong
Offer patients with metastatic castrate-resistant PCa (mCRPC) who are candidates for cytotoxic therapy and are chemotherapy naïve docetaxel with 75 mg/m^2 every three weeks.	Strong
Offer patients previously untreated for mCRPC and harbouring an *HRR* or breast cancer gene (*BRCA*) mutation abiraterone in combination with olaparib if the patient is fit for both agents and did not previously receive an ARPI.	Strong
Offer patients previously untreated for mCRPC and harbouring a *BRCA* mutation abiraterone in combination with niraparib if the patient is fit for both agents and did not previously receive an ARPI.	Strong
Offer patients previously untreated for mCRPC and harbouring an *HRR* mutation enzalutamide in combination with talazoparib, if the patient is fit for both agents and did not previously receive an ARPI.	Strong
Offer genetically tested patients without known *HRR* mutations and previously untreated for mCRPC enzalutamide in combination with talazoparib, if the patient is fit for both agents, willing to bear additional side effects, and did not previously receive an ARPI.	Weak
Offer poly(ADP-ribose) polymerase (PARP) inhibitor monotherapy to pretreated mCRPC patients with relevant DNA repair gene mutations.	Strong
Offer patients with mCRPC and progression following docetaxel chemotherapy further life-prolonging treatment options, which include abiraterone, cabazitaxel, enzalutamide, radium-223 and olaparib in case of DNA *HRR* alterations.	Strong
Base further treatment decisions regarding mCRPC on PS, previous treatments, symptoms, comorbidities, genomic profile, extent of disease, and patient preference.	Strong
Offer cabazitaxel to patients previously treated with docetaxel.	Strong
Offer cabazitaxel to patients previously treated with docetaxel who have progressed within 12 months of treatment with abiraterone or enzalutamide for mCRPC.	Strong
Offer enzalutamide plus radium-223 to asymptomatic or mildly symptomatic mCRPC patients with bone metastases without visceral metastases.	Strong
Offer ^{177}Lu-PSMA-617 to ARPI and docetaxel pretreated mCRPC patients with one or more metastatic lesions, highly expressing prostate-specific membrane antigen (PSMA) on diagnostic radiolabelled PSMA positron emission tomography/computed tomography (PET/CT) scan and lacking any relevant non-PSMA avid metastases.	Strong
Offer ^{177}Lu-PSMA-617 to ARPI pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on diagnostic radiolabelled PSMA PET/CT scan, if not fit for docetaxel.	Weak

6.7.15 *Recommendation for non-metastatic castrate-resistant disease*

Recommendation	Strength rating
Offer apalutamide, darolutamide or enzalutamide to patients with M0 castrate-resistant PCa and a high risk of developing metastasis (prostate-specific antigen doubling time < 10 months) to prolong time to metastases and overall survival.	Strong

Figure 6.4: Treatment of non-metastasized (M0) – asymptomatic



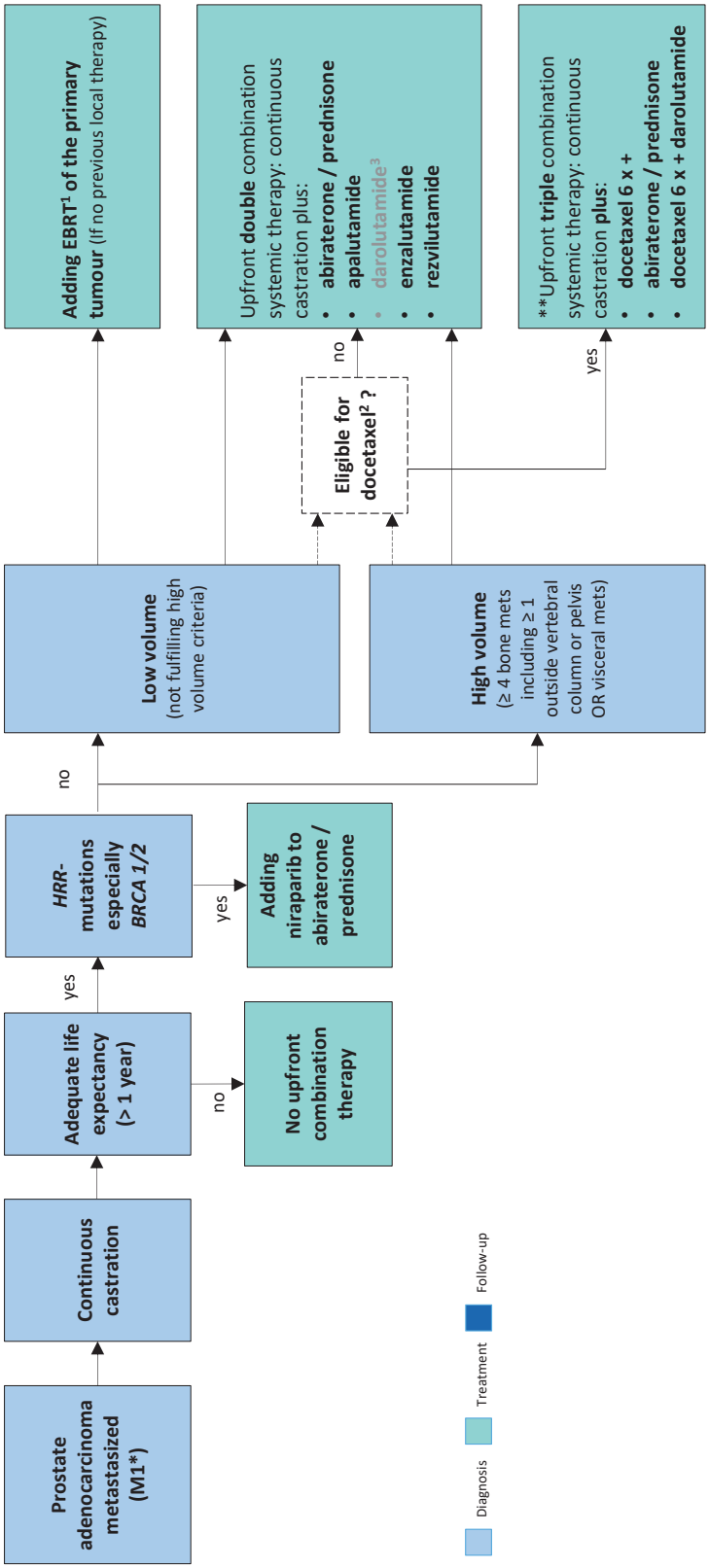
** Life expectancy ten years.*
*** Recommendation based on clinical staging using digital rectal examination, not imaging.*
**** Recommendation based on staging using combination of bone scan and CT.*
***** See text, dependent on GG and (biopsy) volume.*

[1] *EBRT: IMRT/VMAT + IGRT of the prostate.*

= weak recommendation.

ADT = androgen deprivation therapy; CT = computed tomography; DRE = digital rectal examination; EBRT = external beam radiotherapy; ECE = extracapsular extension; ePLND = extended pelvic lymph node dissection; GG = grade group; HDR = high-dose rate; IDC = intraducal carcinoma; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; LDR = low-dose rate; PSA = prostate-specific antigen; VMAT = volumetric modulated arc therapy.

Figure 6.5: Treatment of metastasized (M1*) – disease, M+HSPC



** Based on staging using combination of bone scan and CT.*
***Not for low volume, metachronous disease.*
[1]EBRT: IMRT/VMAT + IGRT of the prostate (equivalent of up to 72 Gy in 2 Gy fractions).
[2]Triple therapy was better than ADT plus docetaxel but randomised data comparing it to ADT plus ARTA is missing.
[3]Darolutamide is shown in grey due to it being a weak recommendation.
ARPI = androgen receptor pathway inhibitors; ADT = androgen deprivation therapy; BRCA = breast cancer gene; CT = computed tomography; EBRT = external beam radiotherapy; HSPC = hormone-sensitive metastatic prostate cancer; HRR = homologous recombination repair; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; VMAT = volumetric modulated arc therapy.
Note: Please be aware that the various options in the following flowcharts present a generalised approach only and cannot take the management of individual patients into account, nor the availability of resources.

7. FOLLOW-UP

The rationale for following up patients is to assess immediate and long-term oncological results, to ensure treatment compliance, and to allow initiation of further therapy, when appropriate. In addition, follow-up allows monitoring of side effects or complications of therapy, functional outcomes and an opportunity to provide psychological support to PCa survivors, all of which is covered in Chapter 8.

For patients, the most critical aspect of PCa is the diagnosis, the ensuing treatment and follow-up. These must be discussed between the patient and the clinician to arrive at a shared decision on the treatment and the planned follow-up, including modalities, periodicity and how this will be communicated to the patient. The patient must be prepared for various potential outcomes of the follow-up, e.g. PSA levels, and what to expect from these. Otherwise, even a very small increase in PSA levels can cause unnecessary fear, even panic.

7.1 Watchful waiting

Watchful waiting refers to conservative management for patients deemed unsuitable for curative treatment from the outset, and patients are clinically 'watched' for the development of local or systemic progression with (imminent) disease-related complaints, at which stage they are then treated palliatively according to their symptoms to maintain or improve QoL (see Section 6.2.1).

7.2 Active surveillance strategy

Patients included in an AS programme must be monitored according to the recommendations presented in Section 6.2.1.c.

7.3 Follow-up: After local treatment with curative intent

*7.3.1 **Definition***

Local treatment is defined as RP or RT, either by IMRT plus IGRT or LDR- or HDR-BT or any combination of these, including neoadjuvant and adjuvant hormonal therapy. Unestablished alternative treatments such as HIFU, cryosurgery and focal therapy options do follow the general principles as presented in this section. In general, a confirmed rising PSA is considered a sign of disease recurrence.

*7.3.2 **Why follow-up?***

The first post-treatment clinic visit focuses on detecting treatment-related complications and assisting patients in coping with their new situation, apart from providing information on the pathological analysis. Men with PCa are at increased risk of depression and attention to mental health status is required [1434, 1435]. Tumour or patient characteristics may prompt changing the follow-up schedule. Follow-up also allows the introduction of additional/salvage treatments should that be considered necessary given the expected life-expectancy, patient symptoms and EAU risk categories for biochemical recurrence (see 6.1 and Table 4.3)

*7.3.3 **How to follow up?***

The procedures indicated at follow-up visits vary according to the clinical situation. A disease-specific history is mandatory at every follow-up visit and includes psychological aspects, signs of disease progression, and treatment-related complications. Evaluation of treatment-related complications in the post-treatment period is highlighted in Section 8.2. The examinations used for cancer-related follow-up after curative surgery or RT are discussed below.

7.3.3.a Prostate-specific antigen monitoring

Measurement of PSA is the cornerstone of follow-up after local treatment. While PSA thresholds depend on the local treatment used, PSA recurrence almost always precedes clinical recurrence [1436, 1437]. The key question is to establish when a PSA rise is clinically significant since not all PSA increases have the same clinical value (see Section 6.4.2) [994]. No prospective studies are available on the optimal timing for PSA testing and the impact on oncological outcomes.

7.3.3.a.1 Prostate-specific antigen monitoring after radical prostatectomy

Following RP, the PSA level is expected to be undetectable. Biochemical recurrence is any rising PSA after prostatectomy as defined in Section 6.3.6. Prostate-specific antigen level is expected to be undetectable two months after an RP [1438]. Prostate-specific antigen is generally determined every six months for a period of three years and yearly thereafter, but the evidence for a specific interval is low [612] and based mainly on the observation that early recurrences are more likely to be associated with more rapid progression [994, 1439, 1440]. A rising PSA may occur after longer intervals up to 20 years after treatment and depends on the initial risk group [934]. A yearly PSA after three years is considered adequate, given that a longer interval to BCR is correlated with a lower EAU-BCR risk score but approximately 50% of recurrence should be expected beyond three years. Follow-up should be terminated if life expectancy drops < 10 years. As indicated in Section 6.4.2 no definitive threshold can be given for relapse after RP. Persistently measurable PSA in patients treated with RP is discussed in Section 6.3.6.

Ultrasensitive PSA assays remain controversial for routine follow-up after RP. Men with a PSA nadir < 0.01ng/mL have a high (96%) likelihood of remaining relapse-free within two years [1441]. In addition, post-RP PSA levels > 0.01ng/mL in combination with clinical characteristics such as ISUP GG and surgical margin status may predict PSA progression and can be useful to establish follow-up intervals [1440]. However, up to 86% of men were reported to have PSA values below 0.2ng/mL at five years after an initial PSA nadir below 0.1ng/mL within six months after surgery [1442].

7.3.3.a.2 Prostate-specific antigen monitoring after radiotherapy

Following RT, PSA drops more slowly as compared to post-RP. A PSA nadir < 0.5ng/mL is associated with a favourable outcome after RT, although the optimal cut-off value remains controversial [1443]. The interval before reaching the PSA nadir can be up to three years or more. At the 2006 RTOG-ASTRO Consensus Conference, the Phoenix definition of radiation failure was proposed to establish a better correlation between definition and clinical outcome (mainly metastases), namely an increase of 2ng/mL above the post-treatment PSA nadir [1016]. This definition also applies to patients who received ADT [1016].

7.3.3.b Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level, although very rarely [1444]. This has only been proven in patients with unfavourable, undifferentiated tumours. Prostate-specific antigen and DRE comprise the most useful combination for first-line examination in follow-up after RT, but the role of DRE was questioned since it failed to detect any local recurrence in the absence of a rising PSA in a series of 899 patients [1445]. In a series of 1,118 prostatectomy patients, no local histologically proven recurrence was found by DRE alone and PSA measurement may be the most efficient test required after RP [1446, 1447].

7.3.3.c Transrectal ultrasound, bone scintigraphy, CT, MRI and PET/CT

Imaging techniques have no place in routine follow-up of localised PCa, as long as the PSA is not rising and patients are asymptomatic. Imaging is only justified in patients for whom the findings will affect treatment decisions, either in case of BCR or in patients with symptoms.

7.3.3.d Functional follow-up

All local treatments for PCa may cause short- and long-term side effects of various degree that will affect the patients' QoL. For quality control, and to help the patient in choosing the optimal treatment for him, it is essential that the functional outcomes of any treatment are measured and registered by validated and reproducible methods. To address side effects and their impact on QoL, specific tools or 'patient-reported outcome measures' (PROMs) have been developed and validated for men with PCa. These questionnaires assess common issues after PCa diagnosis and treatment and generate scores that reflect the impact on perceptions of HRQoL. For further discussion on this, see Section 8.3.

7.3.4 How long to follow-up?

Most patients who fail treatment for PCa do so within seven years after local therapy [1448]. Patients must be followed more closely during the initial post-treatment period when risk of failure is highest. Prostate-specific antigen measurement and disease-specific history are recommended every six months for a period of three years, and then annually. Whether follow-up should be stopped if PSA remains undetectable (after RP) or stable (after RT) remains an unanswered question, but it seems fair that follow-up is only done to the point that, if a recurrence is found, the patient is fit enough for salvage therapy.

Risk assessment to predict metastases-free and PCa-specific survival after recurrence after primary treatment may guide individual decisions on a need for longer follow-up [939, 994, 1449]. Even in men with a PSA-DT less than ten months after RP who choose to defer treatment, a median MFS of 192 months and OS of 204 months from RP was observed, indicating the relatively long disease-free intervals observed in men with a rising PSA after local treatment [1450].

Symptomatic recurrence without a PSA rise is extremely rare, however, the symptoms typical for recurrent disease may vary and are poorly defined by published data. In case of the following symptoms, PSA testing should be performed to exclude a possible cancer recurrence, in particular in men not followed up by regular testing of their PSA levels: pelvic/skeletal pain, haematuria, progressive LUTS, progressive lower body oedema, progressive bowel complaints or complaints of fatigue, sarcopenia or unexplained weight loss [1451].

7.3.5 Summary of evidence and recommendations for follow-up after treatment with curative intent

Summary of evidence	LE
A detectable PSA indicating a relapse of the disease must be differentiated from a clinically meaningful relapse. The PSA threshold that best predicts further metastases after RP is > 0.4ng/mL and > NADIR + 2ng/mL after IMRT/VMAT plus IGRT (± ADT].	3

Recommendations	Strength rating
Routinely follow-up asymptomatic patients by obtaining at least a disease-specific history and a prostate-specific antigen measurement.	Strong
At recurrence, only perform imaging if the result will affect treatment planning.	Strong

7.4 Follow-up: During first line hormonal treatment (androgen sensitive period)

7.4.1 Introduction

Androgen deprivation therapy is used in various situations: combined with RT for localised or locally advanced disease for relapse after a local treatment, or in the presence of metastatic disease in combination with other treatments. All these situations are based on the benefits of testosterone blockage or suppression either by drugs (LHRH agonists or antagonists) or orchidectomy. In the majority of patients with metastatic PCa, castrate resistance will develop, which is defined as PCa progression despite a testosterone level < 50ng/dL.

This section addresses the general principles of follow-up of patients on ADT alone. Section 6.5.3 includes further information on other drug treatments. In addition, the specific follow-up needed for every single drug is outside the scope of this text, as is follow-up after chemotherapy.

To detect disease- and treatment-related complaints, regular clinical follow-up is mandatory and cannot be replaced by imaging or laboratory tests alone.

7.4.2 Purpose of follow-up

The main objectives of follow-up in patients receiving ADT are to ensure treatment compliance, to monitor treatment response, to detect and manage side effects early, and to guide treatment at the time point of clinical progression.

After the initiation of ADT, it is recommended that patients be evaluated every three to six months. This must be individualised, and each patient should be advised to contact his physician in the event of troublesome symptoms. This is even more important for patients who receive a combination of ADT and other potent medication for their disease, e.g. ARPI, where the frequency of follow-up is monthly for the first three months.

7.4.3 General follow-up of men on hormonal therapy

Patients under ADT require regular follow-up, including monitoring of serum testosterone, creatinine, liver function and metabolic parameters at three-to six-month intervals. Men on ADT can experience toxicity independent of their disease stage. Androgen-deprivation therapy induced bone density loss increases the risk of fractures [1452]. Therefore, assessment of bone density before and during treatment with ADT with or without a combination with other drugs is essential.

As the consequences of ADT are so varying, a structured follow-up including lab results, radiology and QoL may be of value both for the patient and for the treating physician [1453].

7.4.3.a Testosterone monitoring

Testosterone monitoring should be considered standard clinical practice in men on ADT. Many men receiving medical castration will achieve a castrate testosterone level (< 20ng/dL), and most will achieve a testosterone level (< 50ng/dL). However, approximately 13–38% of patients fail to achieve these levels, and up to 24% of men may experience temporary testosterone surges (testosterone > 50ng/dL) during long-term treatment [1438] - a condition referred to as 'acute on-chronic effect' or 'breakthrough response' [1454]. Breakthrough rates for the < 20ng/dL threshold were found to be more frequent (41.3%) and an association with worse clinical outcomes was suggested [1454].

The timing of measurements is not clearly defined. A three- to six-month testosterone level assessment has been suggested to ensure castration is achieved (especially during medical castration) and maintained. If a castrate testosterone level is not reached, switching to another agonist or antagonist or to an orchiectomy should be considered. In patients with a confirmed rising PSA and/or clinical progression, serum testosterone must be evaluated in all cases to confirm a castration-resistant state. Suboptimal testosterone castrate levels should Ideally be confirmed with an appropriate assay [1455, 1456]. After ADT cessation (intermittent treatment or temporary ADT use as with EBRT), testosterone recovery is dependent on patient's age, the testosterone levels before start of ADTand the form and duration of ADT [1457, 1458].

7.4.3.b Liver function monitoring

Liver function tests will detect treatment toxicity this is especially applicable for NSAA abiraterone acetate and novel AR antagonists. These tests rarely indicate disease progression but are crucial for monitoring adverse events. Transaminase levels should be checked at least once yearly in all men receiving combined ADT. However, more frequent monitoring is warranted in the first six months after treatment initiation, as liver function abnormalities were most commonly observed during this period in large clinical trials [1459]. The required monitoring frequency may vary depending on the specific drug used, with more intensive monitoring advised for agents known to have higher hepatotoxic potential, such as abiraterone acetate [1460].

7.4.3.c Serum creatinine and haematological parameters

Estimated glomerular filtration rate monitoring is good clinical practice because an increase may be linked to ureteral obstruction or bladder retention. A decline in haemoglobin is a known side effect of ADT. A significant decline after three months of ADT is independently associated with shorter progression-free and OS rates and might explain significant fatigue, although other causes should be considered [1461]. Anaemia is often multifactorial and other possible aetiologies should be excluded. An early decrease in haemoglobin three months after ADT initiation predicted better survival, whereas a decrease beyond six months was associated with poor outcome in the SPCG-5 population [1462].

7.4.3.d Monitoring of metabolic complications

The most severe complications of androgen suppression are metabolic syndrome, cardiovascular morbidity, mental health problems and bone resorption (see Section 8.2.5).

All patients should be screened for diabetes by checking fasting glucose and HbA1c (at baseline and routinely) in addition to checking blood lipid levels. Men with impaired glucose tolerance and/or diabetes should be referred for an endocrine consultation. Prior to starting ADT, an ECG should be done. A cardiology consultation is recommended, as a minimum, in men with a history of cardiovascular disease, and depending on the combination drug planned, also an ECHO. Men on ADT are at increased risk of hypertension and cardiovascular problems; therefore, regular checks are required [1463]. More profound androgen ablation resulted in a higher cardiovascular toxicity [1464] and cardiorespiratory fitness decreased even after six months of ADT [1465].

7.4.3.e Monitoring bone problems

Androgen deprivation therapy increases the risk of osteoporosis. A combination of ADT with apalutamide, darolutamide, enzalutamide, abiraterone plus prednisone or docetaxel increases the fracture risk even further [1245, 1466, 1467]. Administration of ADT for more than a year, as compared to less than one year, showed a higher risk of osteoporosis (HR: 1.77 and 1.38, respectively) [1468]. Several scores (e.g. Fracture Risk Assessment Tool [FRAX score], Osteoporosis Self-Assessment Tool [OST], Osteoporosis Risk Assessment Instrument [ORAI], Osteoporosis Index of Risk [OSIRIS], and Osteoporosis Risk Estimation [SCORE]) can help identify men at risk of osteoporotic complications, but validation of these scores in the ADT setting is required (see Section 8.3.2.b) [1348, 1469, 1470].

Vitamin D and calcium levels should be regularly monitored when patients receive ADT, and patients should be supplemented if required (see Section 8.3.2.b).

Routine bone monitoring for osteoporosis should be performed at the start of ADT using dual emission X-ray absorptiometry (DEXA) scan [1349, 1471, 1472]. Presence of osteoporosis should prompt the use of bone protective agents. The criteria for initiation of bone protective agents are provided in Section 8.3.2.b. If no bone protective agents are given, a DEXA scan should be performed regularly - at least every two years [1473].

A review summarising the incidence of bone fractures showed a near doubling of the risk of fractures when using ADT depending on patients' age and duration and type of ADT with the highest incidence in older men and men on additional novel ARPI medication across the entire spectrum of disease [1474]. In case of an osteoporotic fracture, a bone protective agent is mandatory.

7.4.3.f Monitoring lifestyle, mental health, cognition, fatigue and sexual function

Lifestyle (e.g. diet, exercise, smoking status and so on) affects QoL and potentially outcome [1475]. During follow-up, men should be counselled on the beneficial effects of exercise to decrease ADT-related toxicity [1476]. Androgen deprivation therapy may affect mental and cognitive health and men on ADT are three times more likely to report depression [1477]. Attention to mental health should therefore be an integral part of the follow-up scheme. Men on ADT may experience complaints of fatigue, possibly related to systemic inflammation [1478]. Reduced cognitive performance and fatigue may arise within six months after initiation of ADT but can improve over time [1479]. Another aspect of starting ADT is that it leads to sexual dysfunction, causing > 80% of couples to cease sexual activity completely. This aspect affects patients as well as their partners, and couple counselling should be considered [1480].

7.4.4 Follow-up of patients on ADT (non-metastatic mHSPCa)

7.4.4.a Prostate-specific antigen monitoring

Prostate-specific antigen is a key marker for following the course of androgen-sensitive non-metastasised PCa. Imaging should be considered when PSA is rising > 2ng/mL or in case of symptoms suggestive of metastasis.

7.4.4.b Imaging

The choice of imaging modality is between PSMA-PET/CT, which offers higher sensitivity, and conventional imaging (CI) with CT or MRI and bone scan on which almost all clinical studies and guideline recommendations are based (see Section 5.8). With its higher sensitivity, next-generation imaging may detect progression earlier. Imaging should be scheduled regularly, including in asymptomatic patients with stable PSA, because the earlier recommendation that asymptomatic patients with a stable PSA level do not require further imaging may no longer hold true. This is particularly the case in patients with aggressive variants when PSA levels may not reflect tumour progression [1481]. New bone pain requires at least targeted imaging and potentially a bone scan. When PSA progression suggests CRPC status and treatment modification is considered, imaging, by means of a bone and CT scan, is currently recommended for restaging.

7.4.5 Methods for follow-up in men under ADT for hormone-sensitive metastatic PCa

In metastatic patients, it is of the utmost importance to counsel about early signs of spinal cord compression, urinary tract complications (ureteral obstruction, bladder outlet obstruction) or bone lesions that are at an increased fracture risk. Since most men will receive another anticancer therapy combined with ADT such as ARPI, chemotherapy, local RT, or combinations, follow-up frequency should also be dependent on the treatment modality. A secondary analysis of the Titan study found that nearly half of the patients developing subsequent radiographic progression had no concomitant PSA progression, suggesting that heavy reliance on PSA monitoring may be inadequate for assessing disease activity in this context [1246]. The specific points related to follow-up during the castrate-resistant situation are detailed in Section 6.7.9.

7.4.5.a PSA monitoring

In men on ADT alone, a PSA decline to < 2.4ng/mL suggests a likely prolonged response and follow-up visits can be scheduled every three to six months, provided the patient is asymptomatic or clinically improving. This applies to men on ADT monotherapy as well as after ADT plus docetaxel [1219]. Depending on symptoms and risk assessment, more frequent visits may be indicated. Treatment response may be evaluated based on a change in serum PSA level [1218, 1219] and bone and CT scan, although there is no consensus on how frequently these scans should be performed [1414]. A rise in PSA level usually precedes the onset of clinical symptoms by several months. A rising PSA should prompt assessment of testosterone level, which is mandatory to define CRPC status, as well as restaging using imaging. However, it is now recognised that a stable PSA during ADT is not enough to characterise a nonprogressive situation [1482]. In addition, during the combination of ADT and ARPI treatment, reliance on PSA without regular imaging might miss early detection of progressive PCa because a secondary analysis of the Titan study found that nearly half of the patients developing subsequent radiographic progression had no concomitant PSA [1246].

7.4.5.b Imaging as a marker of response in metastatic PCa

Treatment response in soft-tissue metastases can be assessed by morphological imaging methods using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, these criteria cannot be used for bone metastases in which response assessment is difficult [1483, 1484].

When bone scan is used to follow bone metastases, a quantitative estimation of tracer uptake at bone scan can be obtained through automated methods such as the Bone Scan Index [1485]. Nonetheless, bone scan is challenging due to the so-called 'flare' phenomenon, which is defined by the treatment-induced demasking of earlier invisible metastases. This 'flare' actually represents a favourable response when observed within eight to twelve weeks of treatment initiation. The differentiation between progression of bone metastases and this 'flare' requires repeated bone scans. Computed tomography cannot be used to monitor sclerotic bone lesions because bone sclerosis can occur under effective treatment and reflects bone healing. Magnetic resonance imaging can directly assess the bone marrow and demonstrate progression based on morphologic criteria or changes in apparent diffusion coefficient. A standardisation for reporting is available [1486]. The ability of PET/CT to assess response has been evaluated in a number of studies. Until additional data are available, MRI and PET/CT should not be used outside trials for treatment monitoring in metastatic patients [1487].

In the absence of a PSA rise, men with metastasised PCa on ADT should also be followed up with regular imaging, since twenty-five percent of men with or without docetaxel in the CHAARTED trial developed clinical progression without a PSA rise [1482]. One in eight men with a PSA < 2ng/mL showed clinical progression [1482]. The addition of docetaxel to ADT in the CHAARTED trial population did not reduce the incidence of clinical progression at low PSA values and this rate was similar for both low- and high-volume disease according to the CHAARTED criteria [1482]. In addition, during the combination of ADT and ARPI treatment in mHSPC, reliance on PSA without regular imaging might miss early detection of progressive PCa because a secondary analysis of the Titan study found that nearly half of the patients developing subsequent radiographic progression had no concomitant PSA progression [1246]. In the Prevail study, nearly one-quarter of mCRPC patients on enzalutamide had radiographic progression without increasing PSA [1488]. However, the optimal timing and image modality to be used remain unclear, as does the real clinical value of any findings.

7.4.6 Recommendations for follow-up during hormonal treatment

Recommendations	Strength rating
The follow-up strategy must be individualised based on stage of disease, prior symptoms, prognostic factors and the treatment given.	Strong
In patients on long-term androgen deprivation therapy (ADT), measure initial bone mineral density to assess fracture risk.	Strong
In patients receiving combination treatment, offer bone protection to avoid fractures.	Strong
In patients with stage M0 disease, schedule follow-up at least every six months. As a minimum requirement, include a disease-specific history, serum prostate-specific antigen (PSA) determination, as well as liver and renal function in the diagnostic work-up.	Strong
In M1 patients, schedule follow-up at least every three to six months, including imaging at regular intervals.	Strong
During follow-up of patients receiving ADT, check PSA and testosterone levels and monitor patients for symptoms associated with metabolic syndrome as a side effect of ADT.	Strong

In patients on long-term ADT, as a minimum requirement, include a medical history including assessment of ADT-induced complications, haemoglobin, serum creatinine, alkaline phosphatase, lipid profiles and HbA1c level meas-urements.	Strong
Counsel patients (particularly patients with M1b status) about the clinical signs suggestive of spinal cord compression.	Strong
When disease progression is suspected, restaging is required and the subsequent follow-up must be adapted/individualised.	Strong
In patients with suspected progression, assess the testosterone level. By definition, castration-resistant PCa requires a testosterone level < 50ng/dL (< 1.7nmol/L).	Strong

8. QUALITY OF LIFE OUTCOMES IN PROSTATE CANCER

This chapter is presented in two parts. The first part of this chapter (Section 8.2) summarises long-term consequences (≥ twelve months) of therapies for PCa. Based on two SRs. The second part of this chapter (Section 8.3) provides evidence-based recommendations for supporting patients when selecting primary treatment options for localised disease and supportive interventions aimed at improving disease-specific QoL across all stages of disease.

8.1 Introduction

Quality of life and personalised care go hand in hand. Treating PCa can affect an individual both physically and mentally, as well as close relations and work or vocation. These multifaceted issues all have a bearing on an individual's perception of QoL [1489, 1490]. Approaching care from a holistic perspective requires the intervention of a multidisciplinary team including urologists, medical oncologists, radiation oncologists, oncology nurses, behavioural practitioners and many others, including fellow patients. Attention to the psychosocial concerns of people with PCa is integral to quality clinical care, and this can include the needs of carers and partners [1491]. Prostate cancer care should not be reduced to focusing on the organ in isolation: side effects or late adverse effects of treatment can manifest systemically and have a major influence on the patient's QoL. Psychological distress can be caused by the cancer diagnosis itself, cancer symptoms and/or treatment side effects [1492]. Taking QoL into consideration relies on understanding the patient's values and preferences so that optimal treatment proposals can be formulated and discussed. Cross-sectional patient-reported outcomes studies in general PCa populations show the impact of treatment on global and disease-specific QoL is greater than that described in clinical trial populations, who often have less co-morbidities and belong to higher socio-economic groups. Individuals undergoing two or more treatments have more symptoms and greater impact on QoL [1493, 1494]. Subgroups of people, including those with poor general health, being unmarried, older age and/or pre-existing depressive symptoms, are more at risk of long-term mental health issues following treatment for PCa [1495].

8.2 Adverse effects of PCa therapies

*8.2.1 **Active surveillance***

In an SR [1496] on the long-term (> 5 year) health-related QoL in patients on active surveillance, researchers observed that there were differences in specific functional outcomes between patients on AS and surgery or radiotherapy ≥ five years after treatment. In patients on AS, the overall HRQoL and psychological well-being outcomes were good. All studies comparing AS with active treatment found no substantial or consistent difference in general HRQoL PROMs between groups. In preservation of continence, there is a clear advantage for AS over active treatment, particularly to RP. Results suggest that even after extended periods, continence is still considerably superior in AS to that in RP. Obstructive voiding symptoms were more common in patients on AS than in postoperative patients. In the domain of sexual function, it is seen that AS group has better than or comparable sexual function to that in the active treatment group. Studies comparing AS with that of PCa-free patients had mixed results with papers observing no statistically significant difference and others reporting that sexual function was, at least numerically, worse in patients on AS than in PCa-free patients. All patients on AS report good quality of life, similar to that in individuals without prostate cancer [1497]. Regarding anxiety, it was observed in a registry on active surveillance in the USA that men undergoing active surveillance had a moderate risk of cancer-specific anxiety that significantly decreases over time. Patients considering active surveillance can be informed that, although it is common experience some anxiety initially, most men rapidly adjust and report low levels of anxiety within two years [1497].

8.2.2 *Surgery*

A lack of clear consensus in reporting surgical complications following RP - specifically urinary incontinence and stricture rates - and the introduction of different techniques has resulted in a wide variation in the types of complications reported, as well as variation in the overall incidence of complications [1498-1501]. The most common postoperative complication is ED, but other related issues to consider include dry ejaculation, which occurs with removal of the prostate, change in the quality of orgasm and occasional pain on orgasm. Men also complain of loss of penile length (3.73%, 19/510 men) [1502]. The second most commonly occurring complication is long-term incontinence [1498-1501], but voiding difficulties may also occur that are associated with bladder neck contracture (e.g. 1.1% after RALP) [1503].

A key consideration is whether long-term consequences of surgery are reduced by using newer techniques such as RALP. Systematic reviews have documented complication rates after RALP [735-739], and can be compared with contemporaneous reports after RRP [740]. Based on these reports, the mean continence rates at twelve months were 89–100% for patients treated with RALP and 80–97% for patients treated with RRP. A prospective controlled nonrandomised trial of patients undergoing RP in fourteen centres using RALP or RRP demonstrated that, at twelve months after RALP, 21.3% were incontinent, as were 20.2% after RRP. The unadjusted OR was 1.08 (95% CI: 0.87–1.34). Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. The unadjusted OR was 0.81 (95% CI: 0.66–0.98) [741, 1504]. Further follow-up demonstrates similar functional outcomes with both techniques at 24 months [1504, 1505]. A single-centre randomised phase III study comparing RALP and RRP (n = 326) also demonstrates similar functional outcomes with both techniques at 24 months [1506]. Prostatectomy was found to increase the risk of complaints from an inguinal hernia, particularly after an open procedure when compared to minimally invasive approaches [1507, 1508]. For those undergoing minimally invasive procedures, port-site hernia has been reported in 0.66% after inserting a 12mm bladeless trocar and can occur more rarely with 8mm and 5mm trocars [1509]. Another complication after primary treatment is lower limb and genital lymphedema. An SR found a prevalence of (0-14%) lower limb and (0-1%) genital lymphedema after radical prostatectomy with PLND [533], and between 0-9% and 0-8% in patients after irradiation on the LNs. In the subgroup that underwent pelvic irradiation after staging pelvic LNs dissections, the prevalence of lower limb (18-29%) and genital (2-22%) lymphedema is substantially elevated.

8.2.3 *Radiotherapy*

8.2.3.a Side effects of external beam radiotherapy

Analysis of the toxicity outcomes of the ProtecT trial shows that patients treated with EBRT and six months of ADT report bowel toxicity including persistent diarrhoea, bowel urgency and/or incontinence and rectal bleeding (as described in detail in Section 8.3.1.a) [1510]. Participants in the ProtecT study were treated with 3D-CRT and studies using IMRT demonstrate less bowel toxicity than noted previously with 3D-CRT [1511].

An SR and meta-analysis of observational studies comparing patients exposed or unexposed to RT in the course of treatment for PCa demonstrates an increased risk of developing second cancers for bladder (OR: 1.39), colorectal (OR: 1.68) and rectum (OR: 1.62), with similar risks over lag times of five and ten years. Absolute excess risks over ten years are small (1–4%) but should be discussed with younger patients in particular [1512].

Patient-reported outcomes suggest a temporary drop in the EPIC hormonal and sexual domains when six months of ADT was added to radiotherapy, with a disappearance of any clinical relevant difference at one year [1277, 1513].

8.2.3.b Side effects from brachytherapy

Some patients experience significant urinary complications following implantation such as urinary retention (1.5-22%) - with post-implantation TURP reported as being required in up to 8.7% of cases - and incontinence (0–19%) [1514]. Chronic urinary morbidity is more common with combined EBRT and BT and can occur in up to 20% of patients, depending on the severity of the symptoms before BT. Urethral strictures account for at least 50% of urinary complications and can be resolved with dilation in the majority [832, 839]. Prevention of morbidity depends on careful patient selection and IPSS score, backed up by urodynamic studies.

8.2.4 *Local primary whole-gland treatments other than surgery or radiotherapy*

8.2.4.a Whole-gland treatments

An SR and meta-analysis produced evidence that the rate of urinary incontinence at one year was lower for whole-gland cryotherapy than for RP, but the size of the difference decreased with longer follow-up [853]. No significant difference was seen between cryotherapy versus EBRT in terms of urinary incontinence at one year (< 1%); cryotherapy had a similar ED rate (range 0–40%) to RP at one year. Whole-gland HIFU on the other hand showed lower incontinence rates at one year than RP (OR: 0.06, 95% CI: 0.01–0.48) [853].

8.2.4.b Focal treatments

Over the past decade, prostate cancer has been detected at an earlier stage, with smaller tumours and with more patients potentially suitable for focal therapy [858-860]. Focal therapy is seeking the optimal balance regarding cancer control and functional outcome. A recent SR included data from 5,827 patients across 72 studies covering various energy sources and found evidence that focal therapy has favourable functional outcomes and minimises adverse events [864]. For focal HIFU and cryotherapy, this SR showed pad-free continence rates above 95% and a median decrease of erectile function of only 12%. An SR with only prospective data found that focal ablation showed only 9% reduction in sexual function scores, compared to 43% for whole-gland ablation at one year [865].

8.2.5 Androgen-deprivation therapy

Quality of life

Androgen-deprivation therapy impacts sexual function, mood, depression, cognitive function, as well as the relationship with the patient's partner [1515, 1516]. A meta-analysis of over 7,500 patients confirmed that ADT significantly impairs QoL, particularly emotional, physical, and cognitive functioning, with greater declines seen after six months of treatment [1517].

A small RCT evaluated the QoL at one-year follow-up in patients with PSA-only relapse after primary therapy without evidence of metastasis, comparing various ADT regimens with no treatment. Patients treated by ADT reported a significant decline in spatial reasoning, spatial abilities and working memory, as well as increased depression, tension, anxiety, fatigue and irritability during treatment [1518]. A meta-analysis confirmed that ADT significantly increases fatigue, with greater severity in non-metastatic disease and during prolonged treatment [1519]. Conversely, a prospective observational study with follow-up out to three years failed to demonstrate any association with cognitive decline in men on ADT when compared to men with PCa not treated with ADT and healthy controls [1520]. An SR and meta-analysis found no consistent objective cognitive decline with ADT, but did observe a significant worsening in subjective cognition during hormone therapy. Narrative findings also suggested more subjective complaints with enzalutamide than with abiraterone [1519]. A prospective observational study of locally advanced PCA or BCR after local therapy found that immediate ADT was associated with a lower overall QoL compared to deferred treatment [1521].

The side effects induced by ADT are non-negligible and tend to increase over time, prompting attempts to treat metastatic PCa patients while keeping intact the gonadal function, i.e. physiologic testosterone level. A pooled analysis from the MARCAP Consortium showed that testosterone recovery after ADT and radiotherapy is highly variable and influenced by age, baseline testosterone, and duration of treatment. While testosterone recovery was not linearly associated with MFS, a non-linear benefit was seen with six-month ADT, suggesting that the optimal effective castration period (including treatment duration and the time to testosterone recovery) was approximately 10–11 months in this analysis [1522]. This should be interpreted as an observational finding specific to this study, rather than a prescriptive recommendation for ADT duration.

Metastasis-directed therapy (MDT) for men with oligometastatic PCa is a strategy to avoid, or at least postpone, the initiation of ADT. The period of ADT-free survival or eugonadal PFS has been applied as the endpoint for several studies and future reports on its correlation with QoL are awaited. Eugonadal PFS may be prolonged by MDT as compared to intermittent hormone treatment alone in men with oligometastatic PCa either at primary diagnosis or after recurrence [1281]. The EORTC-GUCG 1532 study used eugonadal PFS as end-point as well and showed that it can be achieved with an ARPI with similar PSA response as ADT [1523].

The three-armed Embark study in patients with biochemical recurrence randomised to receive enzalutamide daily plus leuprolide every twelve weeks (combination group), placebo plus leuprolide (leuprolide-alone group), or enzalutamide monotherapy (monotherapy group) demonstrated that treatment with enzalutamide without ADT is not without toxicities and less effective than the combination of ADT and enzalutamide [1524]. The choice between the different treatment options will depend on each patient's preferences after thorough information by the treating physician.

Different types of ADT

An SR and meta-analysis assessed potential benefits of intermittent versus continuous ADT [1525]. Of note, only a minority of patients with less-aggressive PCa are considered eligible for intermittent ADT. The meta-analysis did not reveal an advantage of continuous over intermittent ADT in PCa-specific mortality and did not show a significant reduction in non-PCa mortality of intermittent versus continuous ADT.

In men with metastatic PCa, ADT must be applied continuously and surgical orchiectomy represents a definitive treatment with similar outcomes as compared to LHRH analogues, as demonstrated in an SR of 15 studies comprising nearly 60,000 men on medical ADT as opposed to close to 5,000 men on surgical ADT [1526]. Surgical ADT is considered cost-effective and might prove beneficial for the patient's well-being, because a retrospective study suggested less reported worry and physical discomfort, better overall health, and a higher likelihood of considering oneself free of cancer than men receiving LHRH agonists continuously. The stage at diagnosis had no effect on health outcomes [1527].

ADT duration reduced the likelihood of testosterone recovery and prolongs the time to recovery significantly. In 1,230 men with localised PCa randomised to RT without ADT or with ADT for 6, 18 or 36 months of normal testosterone was measured in 87% without ADT, 76% after 6 months, 55% after 18 months, and 43% after 36 months of ADT, respectively. Moreover, time to testosterone recovery increased with ADT duration from 0.3, 1.6, 3 and 5 years for the 0-, 6-, 18- or 36-month schedules, respectively [1071]. In general, testosterone recovered faster in otherwise healthy men with a normal baseline testosterone.

The oral LHRH antagonist relugolix achieved a similar castration resistance-free survival (CRFS) as the LHRH agonist leuprolide, with 48-week CRFS rates of 74.3% and 75.3%, respectively [1528]. After cessation of relugolix and leuprolide testosterone, recovery at 48 weeks was achieved by a greater percentage of men (54% vs. 3.2%), as well as more quickly within median 86 versus 112 days for relugolix and leuprolide, respectively.

Balancing risks and benefits

To appropriately balance the risks of PCa and non-PCa mortality, both the PCa tumour aggressiveness and comorbidities of individual patients must be taken into account. The omega score, which is a quantitative measure of the relative risk for cancer-related versus competing mortality events, might assist in assessing these risks when, for example, deciding whether the addition of ADT to RT provides a greater benefit regarding PCa mortality than a threat regarding non-PCa mortality [1529].

In men with metastatic PCa, balancing the intensity of continuous ADT combined with either an ARPI, docetaxel or both is no less challenging. An SR and meta-analysis on the impact of performance status (PS) on oncologic outcomes showed that combination systemic therapies significantly improved OS in patients with worse PS, as well as in those with good PS, while the MFS benefit from ARPI in the nmCRPC setting was more pronounced in patients with good PS than in those with worse PS [1530]. However, because most RCTs are limited to men with PS of either 0 or 1, these findings might not apply to men with PS of ≥ 2.

8.2.5.a Sexual function

Cessation of sexual activity is very common in people undergoing ADT, affecting up to 93% [1531]. Androgen-deprivation therapy reduces both libido and the ability to gain and maintain erections. The management of acquired ED is mostly non-specific [1532].

Using a specific nonvalidated questionnaire, bicalutamide monotherapy showed a significant advantage over castration in the domains of physical capacity and sexual interest (but not sexual function) at twelve months [1533]. A post-hoc analysis including only patients with sexual interest suggested that bicalutamide was associated with better sexual preservation, including maintained sexual interest, feeling sexually attractive [1534], preserved libido and erectile function [1535].

8.2.5.b Hot flushes

Hot flushes are a common side effect of ADT (prevalence estimated between 44–80% of men on ADT) [1531]. They appear three months after starting ADT, usually persist long-term and have a significant impact on QoL.

Serotonin re-uptake inhibitors (e.g. venlafaxine or sertraline) appear to be less effective in reducing hot flushes than hormonal therapies based on a prospective RCT comparing venlafaxine, 75 mg daily, with medroxyprogesterone, 20 mg daily, or cyproterone acetate, 100 mg daily [1536]. After six months of LHRH (n = 919), 311 men had significant hot flushes and were randomised to one of the treatments. Based on median daily hot-flush score, venlafaxine was inferior -47.2% (interquartile range -74.3 to -2.5) compared to -94.5% (-100.0 to -74.5) in the cyproterone group, and -83.7% (-98.9 to -64.3) in the medroxyprogesterone group. Another RCT (n = 78) compared oestradiol (transdermal 0.9mg or 0.1% gel) to placebo. After six months, oestradiol reduced daily hot flushes frequency (mean adjusted difference MAD -1,6, p = 0.04), but the effect on weekly hot flushes was not significant (MAD -19,6 p = 0.11) [1537].

Considering placebo response rates in up to 30% of patients [1538], prospective RCTs are required to document the efficacy of clonidine, veralipride, gabapentin [1539] and acupuncture [1540].

8.2.5.c ADT induced bone fractures

ADT leads to increased bone turnover and decreased bone mineral density (BMD) over time, which significantly elevates the risk of fractures. The relative risk of fractures increases by up to 45% with long-term ADT [1541]. Severe fractures in men are associated with increased mortality [1542], underscoring the importance of early identification of high-risk patients and timely preventive measures. A precise evaluation of BMD should be performed by DEXA, ideally before starting long-term ADT. A low baseline BMD (T-score < -2.5 or < -1, with other risk factors) indicates a high risk of t non-metastatic fracture and causes should be investigated. Other risk factors include increasing age, BMI of 19 or less, history of previous fracture or parent with fractured hip, current smoking, use of glucocorticoids, rheumatoid arthritis, alcohol consumption > two units per day, history of falls and a number of other chronic medical conditions [1543]. Several fracture risk algorithms such as FRAX (Fracture Risk Assessment Tool), OST (osteoporosis self-assessment Tool), ORAI (Osteoporosis Risk Assessment Instrument), OSIRIS (osteoporosis Index of Risk), and SCORE (Osteoporosis Risk Estimation) incorporate BMD and clinical parameters to guide decision-making. However, these tools are not specifically validated in the context of ADT for PCa, and no preferred tool can currently be recommended. Nonetheless, they may still offer indicative value for decision making (see also section 8.3.2.2) [1348, 1469, 1470]. Obesity (defined as > 10% increase in body fat and/or BMI > 30) and sarcopenia up to 3% reduction in lean tissue mass and weight loss are common during the first year of ADT and contribute to an increased fracture risk [1544-1546].

An SR and meta-analysis of 11 studies involving 11,382 men of which 6,536 received enzalutamide, apalutamide, or darolutamide in combination with ADT (or other enzalutamide-based combinations) and 4,846 controls (placebo, bicalutamide, or abiraterone) showed that adding an ARPI to ADT significantly increases the risk of fractures [1547]. The incidence of non-metastatic fractures was 242 (4%) in the enzalutamide/apalutamide/darolutamide group and 107 (2%) in the control group. The use of enzalutamide, apalutamide or darolutamide was associated with an increased risk of fractures: all-grade fracture (RR, 1.59; 95% CI, 1.35-1.89; p < 0.001), and likely grade 3 fracture or greater (RR, 1.71; 95% CI, 1.12-2.63; p = 0.01).

Bicalutamide monotherapy may have a less pronounced effect on BMD; however, its limited oncological efficacy in M1 disease makes it a poor option in this setting [1548, 1549]. The intermittent LHRH agonist modality might be associated with less bone impact [1550].

8.2.5.d Metabolic effects

Lipid alterations are common and may occur as early as the first three months of ADT [1544]. In addition, ADT also decreases insulin sensitivity and increases fasting plasma insulin levels, which is a marker of insulin resistance. In diabetic patients, metformin appears to be an attractive option for protection against metabolic effects based on retrospective analysis [1551], but there is insufficient data to recommend its use in non-diabetic patients.

Metabolic syndrome is an association of independent cardiovascular disease risk factors, often associated with insulin resistance. It is defined by the presence of at least three of the following criteria [1552]:

- waist circumference > 102cm;
- serum triglyceride > 1.7mmol/L;
- blood pressure > 130/80mmHg or use of medication for hypertension;
- high-density lipoprotein (HDL) cholesterol < 1mmol/L; and
- glycaemia > 5.6mmol/L or the use of medication for hyperglycaemia.

The prevalence of a metabolic-like syndrome is higher in men receiving ADT compared with men not receiving ADT [1553]. Androgen-deprivation therapy impairs skeletal muscle health and muscular weakness is a common complaint as early as in the initial months of treatment. Skeletal muscle mass has a strong influence on basal metabolic rate and is in turn heavily influenced by endocrine pathways [1554]. A prospective longitudinal study of 252 men on ADT for a median of 20.4 months reported a progressive decline in lean body mass over time: 1.0% at one year, 2.1% at two years, and 2.4% at three years, which appears more pronounced in men at ≥ 70 years of age [1555].

An SR on the impact of ADT on body composition found ADT had a relatively stable effect on BMI but increased sarcopenia and subcutaneous adipose tissue [1545]. Sarcopenia at baseline, found in 27% of 110 men with mCRPC, significantly predicted severe toxicity and ER visits in men initiating ARPI treatment. Sarcopenia was also a predictor of radiographic progression and overall mortality regardless of treatment type [1556].

8.2.5.e Cardiovascular morbidity

Cardiovascular mortality is a common cause of death in PCa patients [1143, 1557, 1558]. Several studies showed that even short-term ADT (as early as six months) was associated with an increased risk of diabetes mellitus, cardiovascular disease, and myocardial infarction [1559]. The RTOG 92-02 [1560] and 94-08 [1561] trials confirmed an increased cardiovascular risk, unrelated to the duration of ADT and not accompanied by an overall increased cardiovascular mortality. This was confirmed in the 20-year update of the NRG/RTOG 9202 RCT which found no overall increase in CVM with long-term versus short-term ADT, but a significantly higher rate of fatal myocardial infarctions in men with baseline CVD [1562]. No increase in cardiovascular mortality has been reported in either a secondary analysis of PLCO trial, even among subgroups with pre-existing cardiovascular disease [1563], and in a meta-analysis including the trials RTOG 8531, 8610, 9202, EORTC 30891 and EORTC 22863 [1564]. However, methodological concerns have been raised about this meta-analysis, particularly regarding insufficient adjustment for bias in the included studies [1565, 1566]. A meta-analysis of observational data reports consistent links between ADT and the risk of cardiovascular disease patients treated for PCa, e.g. the associations between LHRH agonists and non-fatal or fatal myocardial infarction or stroke RR: 1.57 (95% CI: 1.26–1.94) and RR: 1.51 (95% CI: 1.24–1.84), respectively [1567]. In an updated meta-analysis on cardiometabolic effects of ADT, ADT was not significantly associated with metabolic syndrome RR: 1.60 (95% CI: 1.06-2.42), had a lower association with diabetes RR 1.43 (95% CI: 1.28-1.59) as previously reported, and an increased risk of hypertension by 30%, RR 1.30 (95% CI: 1.08-1.55). After adjustment for publication bias ADT was associated with a 25% increased risk for diabetes but was not found to be associated with metabolic syndrome [1568].

An increase in cardiovascular mortality has been reported in patients suffering from previous congestive heart failure or myocardial infarction in a retrospective database analysis [1569] or presenting with a metabolic syndrome [1570]. It has been suggested that antagonists might be associated with less CMV compared to agonists, but there is as yet no definite evidence [1571, 1572]. In a phase III RCT, the use of relugolix, an oral LHRH antagonist, was associated with a reduced risk of major adverse cardiovascular events when compared to leuprolide, an injectable LHRH agonists, at 2.9% versus 6.2%, respectively, over a follow-up time of 48 weeks (HR 0.46, 95% CI: 0.24–0.88) [1160]. An SR, including the above RCT, assessing major cardiovascular events in 11 studies comprising approximately 4,200 patients showed a significantly lower risk (HR 0.57 (95% CI: 0.37-0.86) for the antagonist as compared to various agonists, whereas there was no significant difference in all-cause mortality (HR 0.58, 95% CI: 0.32-1.08) [1573].

Concerns about LHRH agonists resulted in an FDA warning and consensus paper from the American Heart Association, American Cancer Society, and American Urological Association [1142]. Preventive advice includes non-specific measures such as loss of Weight, increased exercise, minimising alcohol intake, improved nutrition and smoking cessation [100, 1574].

The adverse events of various ARPI (abiraterone, apalutamide, darolutamide, enzalutamide) in the treatment of mCRPC, nmCRPC and mHSPC were systematically reviewed in a multivariate network meta-analysis. Here, it is suggested that the ARPI adverse effect profiles do not significantly differ from each other, except that enzalutamide was ranked the most toxic with regard to hypertension in mCRPC and nmCRPC, and the most toxic with regard to headache across all PCa settings [1575].

An additional SR and network meta-analysis compared the cardiotoxicity profiles of ARPI across disease states [1576]. Enzalutamide and abiraterone (with prednisone) were associated with higher risks of hypertension, vascular events, and arrhythmias compared to darolutamide, which showed a more favourable cardiovascular safety profile. Bayesian modelling suggested that prior treatment exposure may influence toxicity risk, particularly in men with mCRPC. In men with cardiovascular comorbidities, a darolutamide-based regimen may therefore be preferable. A separate RCT-only meta-analysis of over 22,000 patients confirmed that ARPI significantly increase the risk of cardiovascular events, particularly hypertension (RR 1.69), ischemic heart disease (RR 1.84), and arrhythmias (RR 1.38); although this did not translate into increased cardiac mortality [1577].

8.2.5.f Fatigue

Fatigue often develops as a side effect of ADT, for which regular exercise appears to be the best protective measure. Reporting clinically significant fatigue is associated with severe psychological distress and should prompt screening for anxiety and/or depression [1578]. Anaemia may be a cause of fatigue [1531, 1579]. If present, anaemia requires further evaluation to identify the cause (medullar invasion, renal insufficiency, iron deficiency, chronic bleeding) and treatment should be individualised. Regular blood transfusions may be required in patients with severe anaemia.

8.2.5.g Neurological side effects

Castration also appears to be associated with an increased risk of stroke [1580], and is suspected to be associated with an increased risk for depression and cognitive decline such as Alzheimer disease [1581].

8.2.6 Osteonecrosis during bisphosphonates or denosumab

Bisphosphonates are synthetic pyrophosphate analogues used in the treatment of conditions such as bone malignancy and osteoporosis. Infrequent side effects associated with bisphosphonate use include pyrexia, renal function impairment, hypocalcemia and avascular osteonecrosis of the jaw. Denosumab is a human monoclonal antibody that is used in the treatment of osteoporosis and bone metastasis [1582, 1583]. It acts by inhibiting osteoclast activity, reducing bone resorption, and increasing bone density [1582]. The highly specific mechanism of action of denosumab is the inhibition of receptor activator of nuclear factor-kappa B ligand (RANKL). Denosumab has been shown to be effective at increasing bone mineral density and decreasing the risk of fractures in men with prostate cancer on ADT [1584].

Both drugs are associated with osteonecrosis of the jaw (ONJ). According to the American Society of Bone and Mineral Research, ONJ is described as exposed bone in the maxillofacial region that does not heal within eight weeks of being identified by a healthcare provider in a patient that is currently or has been on bisphosphonates and who does not have a history of radiation therapy in the craniofacial region [1585]. The incidence of ONJ is related to the dose and duration of treatment. The risk ranges from greater than 1% at twelve months to 11% after four years of treatment. Using zoledronic acid alone increases the risk of osteonecrosis to 21% after the third year. An SR on denosumab [1586] showed that, in a total of 8,963 patients with a variety of solid tumours in seven randomised controlled trials (RCTs), the overall incidence of ONJ in patients with cancer receiving denosumab was 1.7% [95% CI: 0.9–3.1%]. The use of denosumab was associated with a significantly increased risk of ONJ in comparison with bisphosphonates (BPs)/placebo treatment (RR 1.61, 95% CI: 1.05–2.48, P = 0.029). Subgroup analysis based on controlled therapies demonstrated an increased risk of ONJ in denosumab therapy, when compared with BPs (RR 1.48, 95% CI: 0.96–2.29, p = 0.078) or placebo (RR 16.28, 95% CI: 1.68–158.05, p = 0.017). Similar results were observed for prostate cancer (RR 3.358, 95% CI: 1.573–7.166, p = 0.002). Concomitant risk factors such as dental extraction, poor oral hygiene, use of removable apparatus, and chemotherapy may further increase the risk of ONJ. Therefore, before starting these drugs, patients should undergo a dental examination and maintain good oral hygiene.

8.3 Overall quality of life in men with PCa

Living longer with PCa does not necessarily equate to living well [1489, 1491]. There is clear evidence of unmet needs and ongoing support requirements for some individuals and partners after diagnosis and treatment for PCa [1587, 1588]. Fear of cancer recurrence and PSA anxiety has a prevalence of 16% and 22%, respectively, across studies [1589]. Combined cognitive- and education-based psychological interventions improve depression, anxiety and distress [1590]. Cancer impacts on the wider family and cognitive behavioural therapy can help reduce depression, anxiety and stress in caregivers [1591]. Radical treatment for PCa can negatively impact long-term QoL (e.g. sexual, urinary and bowel dysfunction), as can ADT used in short- or long-term treatment, e.g. sexual problems, fatigue, psychological morbidity, adverse metabolic sequelae and increased cardiovascular and bone fracture risk [1516, 1592]. Direct symptoms from advanced or metastatic cancer, e.g. pain, hypercalcaemia, spinal cord compression and pathological fractures, also adversely affect health [1593, 1594]. Patients' QoL including domains such as sexual function, urinary function and bowel function is worse after treatment for PCa compared to non-cancer controls [1595, 1596]. A PCa diagnosis commonly results in financial strain both for the individual and their families. This financial toxicity is associated with younger age at diagnosis, Black race, low socioeconomic status, low educational attainment and living in a rural area. Clinicians should discuss financial strains and signpost to support services so that quality of life and adherence to treatment can be maintained [1597].

As QoL is subjective and can mean different things to different people and can be difficult to measure and compare. Nevertheless, there are a number of generally common features across virtually all patients. Drawing from these common features, specific tools or PROMs have been developed and validated for men with PCa. These questionnaires assess common issues after PCa diagnosis and treatment and generate scores that reflect the impact on perceptions of HRQoL. During the process of undertaking two dedicated SRs relating to cancer-specific QoL outcomes in patients with PCa as the foundation for our Guideline recommendations, several validated PROMs were identified in our searches (see Table 8.3.1). The tools with the best evidence for psychometric properties and feasibility for use in routine practice and research settings to assess PROMs in patients with localised PCa were EORTC QLQ-C30 and QLQ-PR25. Because EORTC QLQ-C30 is a general module that does not directly assess PCa-specific issues, it should be adopted in conjunction with the QLQ-PR25 module [1598].

Table 8.3.1: PROMs assessing cancer-specific quality of life [1598]

Questionnaire	Domains/items
European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) [1599]	Five functional scales (physical, role, cognitive, emo-tional and social); three symptom scales (fatigue, pain and nausea and vomiting); global health status/QoL scale; and various single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.
European Organisation for Research and Treatment of Cancer QLQ-PR 25 (EORTC QLQ-PR 25) [1600]	Urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function.
Functional Assessment of Cancer Therapy-General (FACT-G) [1601]	Physical well-being, social/family well-being, emo-tional well-being, and functional well-being.
Functional Assessment of Cancer Therapy-Prostate (FACT-P) [1602]	12 cancer-site-specific items to assess for prostate-related symptoms. Can be combined with FACT-G or reported separately.
Expanded prostate cancer index compo-site (EPIC) [1603]	Urinary, bowel, sexual and hormonal symptoms.
Expanded prostate cancer index compo-site short form 26 (EPIC 26) [1604]	Urinary, sexual, bowel and hormonal domains.
UCLA Prostate Cancer Index (UCLA PCI) [1605]	Urinary, bowel and sexual domains.
Prostate Cancer Quality of Life Instru-ment (PCQoL) [1606]	Urinary, sexual and bowel domains, supplemented by a scale assessing anxiety.
Prostate Cancer Outcome Study Instru-ment [1596]	Urinary, bowel and sexual domains.

8.3.1 Long-term (> twelve months) quality of life outcomes in men with localised disease

8.3.1.a Men undergoing local treatments

In the updated results of the ProtecT trial [1607], treatment-received analyses revealed different impacts of treatments over six years. Men remaining on AM experienced gradual declines in sexual and urinary function with age with increases in ED from 35% at baseline to 53% at six years and nocturia from 20% to 38%. Radical treatment impacts were immediate and continued over six years. After RP, 95% reported ED persisting for 85% at six years, while after EBRT this was 69% and 74%, respectively ($p < 0.001$ compared with AM). After RP, 36% reported urinary leakage requiring at least one pad/day, persisting for 20% at six years, compared with no change in men receiving EBRT or AM ($p < 0.001$). Worse bowel function and bother such as bloody stools (6% at six years) and faecal incontinence (10%) was experienced by more men after EBRT than after RP or AM ($p < 0.001$), with pronounced effects following BT. No treatment affected mental or physical QoL. Another paper on the twelve-year outcome of this trial [1510] showed that the generic quality-of-life scores were similar in randomised groups over seven to twelve years, and 18-24% of patients experienced urinary leakage requiring pads in the prostatectomy group over seven to twelve years, compared with 9-11% in the AM group and 3-8% in the radiotherapy group. Erections sufficient for intercourse were reported in 18% at seven years in the prostatectomy group, compared with 30% in the AM and 27% in the radiotherapy groups. All converged to low levels of potency by year twelve. Nocturia (voiding at least twice per night) occurred in 34% in the prostatectomy group, compared with 48% in the radiotherapy group and 47% in the AM group at twelve years. Faecal leakage affected 12% in the radiotherapy group, compared with 6% in the other groups by year twelve. The AM group experienced gradual age-related declines in sexual and urinary function, avoiding radical treatment effects unless they changed management. The PACE-A Trial randomised 123 patients over 10 years to prostatectomy or SBRT [1608]. At 24 months, only 32 patients in the surgery group and 46 of the RT group were available for analysis. Each group has one patient with more than one security pad per day. In summary, the authors show an equal urinary bother score, with more imitative symptoms and bowel symptoms for SBRT. The overall sexual function is better in the SBRT group. However, this study showed a differential dropout with only 50% patients of the surgery group in the final readout - an extremely show recruitment and an unmet target size.

Other observational studies [785, 1448, 1501, 1609-1612] also report findings regarding RP and RT. The Prostate Cancer Outcomes Study (PCOS) looked at a cohort of 1,655 men, of whom 1,164 had undergone RP and 491 RT [1501]. The study reported that, at five years of follow-up, men who underwent RP had a higher prevalence of urinary incontinence and ED, while men treated with RT had a higher prevalence of bowel dysfunction. However,

despite these differences detected at five years, there were no significant differences in the adjusted odds of urinary incontinence, bowel dysfunction or ED between RP and RT at fifteen years. Investigators have reported that, although EBRT was associated with a negative effect in bowel function, the difference in bowel domain score was below the threshold for clinical significance twelve months after treatment [1511]. As 81% of patients in the EBRT arm of the study received IMRT, these data suggest that the risk of side effects is reduced with IMRT compared to older 3D-CRT techniques. This is supported by a five-year prospective, population-based cohort study in which PROMs were compared in men with favourable and unfavourable risk localised disease [1611]. In the 1,386 men with favourable risk, comparison between AS and nerve-sparing prostatectomy, EBRT or LDR BT demonstrates that surgery is associated with worse urinary incontinence at five years and sexual dysfunction at three years when compared to AS. External beam RT is associated with changes not clinically different from AS, and LDR BT is associated with worse irritative urinary, bowel and sexual symptoms at one year. In 619 men with high-risk localised disease, comparison between non-nerve-sparing RP and EBRT with ADT demonstrates that surgery is associated with worse urinary incontinence and sexual function through five years. An SR demonstrates that the risk of post-radiotherapy ED has reduced to a median of 25% at two years with utilisation of IMRT and is now similar to that noted after LDR BT [1613].

A number of prospective studies have reported specific long-term urinary functional outcomes after RP and RT, even if the studies are not comparative between the two treatment modalities. Considering incontinence and ED after RP, the prospective randomised PIVOT trial, comparing RP to observation, reported that 40% of men wore pads, 20% of whom wore more than > one pad/day, and an increased rate of ED in the RP group as compared to observation from 70% to approximately 87% after a median follow-up of 12.7 years [1448]. The corresponding figures from the prospective non-randomised LAPPRO-trial, comparing open to robot-assisted RP, showed 27–29% of the patients reporting urinary incontinence of some degree after eight years and 66–70% reporting ED [1612]. Data on urinary, sexual and bowel function after RT has been reported from the HYPO-RT-PC trial, a prospective randomised noninferiority trial comparing ultra-HFX to conventional fractionation RT. In this trial, 52–55% of the patients reported urinary problems (RTOG toxicity grade ≥ 1) at five years, of which 4.2–4.7% reported a RTOG grade ≥ 3 urinary morbidity and 7–8% reported moderate-to-severe incontinence at six years. Bowel toxicity of any level (RTOG toxicity grade ≥ 1) was reported in 53–54% of the patients at five years, 1.5–1.9% of whom reported an RTOG grade ≥ 3 bowel morbidity, and 66–71% reported having little or no erection without aids after six-year follow-up [785, 1610].

8.3.1.b Recommendations for quality of life in men undergoing local treatments

Recommendations	Strength rating
Advise patients eligible for active surveillance that global quality of life is equivalent for up to five years compared to radical prostatectomy or external beam radiotherapy (RT).	Strong
Discuss the negative impact of surgery on urinary and sexual function, as well as the negative impact of RT on bowel function with patients.	Strong
Advise patients treated with brachytherapy of the negative impact on irritative urinary symptomatology at one year but not after five years.	Weak

8.3.2 Improving quality of life in men who have been diagnosed with PCa

8.3.2.a Men undergoing local treatments

In men with localised disease, nurse-led multidisciplinary rehabilitation (addressing sexual functioning, cancer worry, relationship issues, depression, and managing bowel and urinary function problems) provided positive short-term effects (four months) on sexual function (effect size 0.45) and long-term (twelve months) positive effects on sexual limitation (effect size 0.5) and cancer worry (effect size 0.51) [1614].

Exercise programs during RT combined with ADT result in consistent benefits for cardiovascular fitness (standardised mean difference [SMD], 0.83; 95% CI: 0.31–1.36; $p < 0.01$) and muscle function (SMD, 1.30; 95% CI: 0.53–2.07; $p < 0.01$) with a reduction in urinary toxicity (SMD, -0.71; 95% CI: -1.25 to -0.18; $p < 0.01$) [1615]. In men undergoing AS, twelve weeks of high-intensity interval training may improve cardiovascular fitness and suppress PSA progression [1616].

In men with post-surgical urinary incontinence, conservative management options include pelvic floor muscle training with or without biofeedback, electrical stimulation, extra-corporeal magnetic innervation (ExMI), compression devices (penile clamps), lifestyle changes, or a combination of methods. Uncertainty relating to the effectiveness and value of these conservative interventions remains [1617]. Surgical interventions

including sling and artificial urinary sphincter (AUS) significantly decrease the number of pads used per day and increase the QoL compared with before intervention. The overall cure rate is approximately 60% and results in improvement in incontinence by approximately 25% [1618]. Other alternatives, such as the Adjustable Transobturator Male System (ATOMS) and the Adjustable Continence Therapy (proACT) may be an option, but appear to be less efficacious than AUS [1619]. For a more detailed overview of management of urinary incontinence in these men, see Chapter 5.6 in the EAU Guidelines for Management of Non-neurogenic Male LUTS [1620].

The use of PDE5 inhibitors in penile rehabilitation has been subject to some debate. A single-centre, double-blind RCT of 100 men undergoing nerve-sparing surgery reported no benefit of nightly sildenafil (50 mg) compared to on-demand use [1621]. However, a multicentre double-blind RCT (n = 423) in men aged < 68 years, with normal pretreatment erectile function undergoing either open, conventional or robot-assisted laparoscopic nerve-sparing RP, tadalafil (5 mg) once per day improved participants' EPIC sexual domain scores (least-squares mean difference +9.6, 95% CI: 3.1–16.0) as compared to 20mg 'on demand' or placebo at nine months of follow-up, even though the difference vanished after the end of study [1622]. Therefore, based on discordant results, no clear recommendation is possible, even if a trend exists for early use of PDE5 inhibitors after RP for penile rehabilitation [1623]. A detailed discussion can be found in the EAU Sexual and Reproductive Health Guidelines [1624].

An SR of genitourinary cancers with mostly prostate cancers makes it evident that sexual well-being concerns for men and their partners are evident from diagnosis and into survivorship. Both patients and partners benefited from interventions but many articulated difficulties with initiating the topic due to embarrassment and limited access to interventions in cancer services [1625].

Testosterone supplementation
Although the evidence is limited, men who are managed expectantly for PCa, or who received radical local therapy, do not have worse outcomes when receiving testosterone supplementation [93]. The panel currently see no contraindication to give testosterone substitution to symptomatic hypogonadal men with prostate cancer where ADT is not the treatment of choice.

8.3.2.b Men undergoing systemic treatments

Similar to men treated with a radical approach, in men with T1-T3 disease undergoing RT and ADT, a combined nurse-led psychological support and physiotherapist-led multidisciplinary rehabilitation programme has reported improvements in QoL. Specifically, this intervention involved action planning concerning patients' needs related to lifestyle changes, weight control, toilet habits, sexuality and psychological problems. This was complemented with pelvic floor muscle therapy. Improvements in urinary (adjusted mean 4.5, 95% CI: 0.6–8.4), irritative (adjusted mean 5.8, 95% CI: 1.4–10.3) and hormonal (adjusted mean 4.8, 95% CI: 0.8–8.8) EPIC domains were found up to 22 weeks of follow-up [1626]. In a three-year follow-up with 92% response rate from the initial study, fewer participants had moderate-to-severe bowel problems in the intervention (n = 2; 3%) versus the control group (n = 10; 14%) (p = 0.016), but the benefits in terms of urinary function were maintained only in those participants with moderate-severe urinary problems at baseline [1627].

Providing supervised aerobic and resistance exercise training of a moderate intensity improves EORTC QLQ-C30 role (adjusted mean 15.8, 95% CI: 6.6–24.9) and cognitive domain outcomes (adjusted mean 11.4, 95% CI: 3.3–19.6), as well as symptom scales for fatigue (adjusted mean 11.0, 95% CI: 20.2–1.7), nausea (adjusted mean 4.0, 95% CI: 7.4–0.25), and dyspnoea (adjusted mean 12.4, 95% CI: 22.5–2.3) up to three months in men treated with ADT [1628]. Such interventions have also reported clinically relevant improvements in FACT-P (mean difference 8.9, 95% CI: 3.7–14.2) in men on long-term ADT [1629, 1630]. These findings are supported by a SR that reported improvements up to twelve weeks in cancer-specific QoL in a meta-analysis of high-quality trials (SMD 0.33, 95%, CI: 0.08–0.58) [1579]. A meta-analysis including 34 studies and 2,741 men confirmed that supervised exercise significantly improves fatigue (SMD –0.32), cancer-specific QoL (SMD 0.24), and muscular strength, with the greatest effects seen in combined aerobic and resistance training [1631]. No relevant adverse effects were reported, and training adherence was high Supervised exercise interventions delivered over twelve months are effective in reducing psychological distress, particularly in those men with the highest levels of baseline anxiety and depression [1632]. In untrained older men, the SR suggests that lower volume exercise programs at moderate-to-high intensity are as effective as higher-volume resistance training for enhancing body composition, functional capacity and muscle strength and may reduce barriers to exercise and enhance adherence [1633].

Another SR and meta-analysis of randomised trials shows that exercise interventions for patients on ADT result in higher lean body mass (mean difference: 0.88, 95% CI 0.4 to 1.36, p < 0.01), a lower body fat mass (mean difference: -0.93, 95% CI: -1.10 to -0.10, p < 0.05), and a lower body fat rate (mean difference:-0.93, 95% CI: -1.39 to -0.47, p < 0.01). Greater efficacy was noted for exercise duration of ≥ six months (versus < six months) and exercise immediately after starting ADT (versus delayed exercise) [1634]. An SR and meta-analysis in patients with prostate cancer undergoing ADT, on supervised exercise therapy versus no therapy shows that supervised exercise therapy is likely superior to no exercise therapy in improving 'disease-specific quality of life' 0.43 (95%CI: 0.29, 0.58) and 'walking performance' −0.41 (95% CI: −0.60, −0.22), with a moderate certainty of evidence [1635]. An SR and meta-analysis focussed on determining the factors that affect adherence to exercise programs found that exercise had no effects (p < 0.05) on quality of life and fatigue. Significant effects (all p < 0.05) were observed for aerobic fitness and upper- and lower-body strength. Adherence to exercise-based interventions was 80.38%, with improvements observed in aerobic fitness and strength. Subgroup analysis revealed exercise adherence impacted fatigue and strength, with greater improvements observed in programs > 12 weeks [1636]. In a prospective randomised trial in frail patients with mCRPC or mHSPC (n = 52), starting enzalutamide at 120mg once daily, instead of the standard 160mg, was associated with significantly less fatigue at 24 weeks (mean difference in FACIT-Fatigue: 6.2; 95% CI: 1.4–11.0) and stable self-reported cognitive function and depressive symptoms, without evidence of reduced PSA response, PFS or OS [1637]. These findings suggest that reduced starting doses of ARSIs may help mitigate treatment-related QoL deterioration in frail patients.

If dietary intake is inadequate, vitamin D and calcium supplementation should be offered, because there is evidence that vitamin D and calcium have modest effects on bone in men on ADT [1621]. Online tools are available to calculate daily calcium intake for individual patients. For vitamin D deficiency, a dose of at least 800 IU/day colecalciferol can be recommended. The use of a 25(OH) assay may be helpful to measure vitamin D levels [1638, 1639].

Antiresorptive therapy is recommended for men on ADT for > six months with either a BMD T-score of < -2.5 or with an additional risk factor for osteoporosis or annual bone loss confirmed to exceed 5%, or in cases of severe fracture. Referral to a bone specialist should be considered in complex cases with severe fracture and/or multiple risk factors. Alendronate, risedronate, zoledronate and denosumab have all been shown to prevent bone loss in men with hormone-sensitive locally advanced and metastatic PCa on ADT [1640-1643]. Patients should be warned about the < 5% risk of osteonecrosis of the jaw and/or atypical femoral fractures associated with these drugs. Therefore before starting these drugs the patients should undergo a dental examination and maintain good oral hygiene. Bisphosphonates increase BMD in the hip and spine by up to 7% in one year [1642, 1644]. The optimal regimen for zoledronic acid for men on ADT with hormone-sensitive locally advanced and metastatic PCa remains unclear: quarterly [1645] or yearly [1646] injections. The question is relevant as the risk of jaw necrosis is both dose- and time-related [1647]. A quarterly regimen should be considered for a BMD ≤ 2.5 as a yearly injection is unlikely to provide sufficient protection [1648, 1649]. Care should be taken when discontinuing treatment because rebound increased bone resorption can occur. A prospective sub-study of the phase III PEACE-1 trial assessed BMD over 24 months in men with *de novo* mCSPC treated with ADT and docetaxel, with or without abiraterone acetate plus prednisone (AAP) [1650]. Bone loss was observed in both arms, but the addition of AAP did not significantly accelerate BMD decline. Osteoporosis was more frequent in the AAP arm (21% vs. 15%), and all reported fractures (n = 4) occurred in this group, although numbers were small and follow-up limited.

In M0 patients, denosumab has been shown to increase the lumbar BMD by 5.6% compared to a 1% decrease in the placebo arm after two years, using 60mg subcutaneous regimen every six months [1584]. This was associated with a significant decrease in vertebral fracture risk (1.5% vs. 3.9%, p = 0.006). The benefits were similar whatever the age (< or > 70 years), the duration or type of ADT, the initial BMD, the patient's weight, or the initial BMI. This benefit was not associated with any significant toxicity, e.g. jaw osteonecrosis or delayed healing in vertebral fractures. In M0 patients, with the use of a higher dosage (120mg every four weeks), a delay in bone metastases of 4.2 months has been shown [1426] without any impact on OS, but with an increase in side effects. Therefore, this higher dose regimen is not recommended.

In the SPARTAN phase III study (apalutamide in nmCRPC) [1651], patients receiving apalutamide experienced falls more frequently versus those receiving placebo (15.6% vs. 9.0%). In the final multivariable model, the baseline patient characteristics of older age, poor ECOG, history of neuropathy and α-blocker use before study treatment remained significantly associated with fall. After-baseline clinical characteristics significantly associated with time to fall were development of neuropathy, arthralgia, and weight loss before fall. To reduce risk of fall, preventive interventions should be considered when the identified baseline conditions and post-treatment neuropathy, arthralgia or weight decrease are present.

8.3.2.c Decision regret

Several treatments with curative intent for localised PCa are available all with comparable ten-year OS [612]. The treatments vary in terms of the incidence of major side effects, including urinary symptoms, bowel symptoms and compromised sexual functioning [1510, 1511, 1652]. For this reason, patients' treatment preferences, in which they weigh expected benefits against likely side effects, are a central consideration in shared decision-making and in making informed treatment decisions [1653-1655].

It remains challenging, however, to evaluate whether the decision-making process can be viewed as successful - that is, whether the choice of treatment best reflects the patient's preferences and expectations [1656, 1657]. According to Decision Justification Theory (DJT), two main components of decision-related regret exist. One is associated with the (comparative) evaluation of the outcome and the second with the feeling of self-blame for having made a poor choice [1658]. Approximately 25% of men with PCa undergoing either single- or combined-modality treatments report experiencing worse side effects than expected [1659]. Urinary incontinence most strongly correlates with regret after prostatectomy [1660].

With the exception of fatigue, unmet expectations are comparable among the treatment groups. Fatigue is less frequently reported as worse than expected by patients who received BT when compared to patients who received RP or EBRT. This could be explained by the less invasive treatment course of BT in comparison to EBRT with or without ADT and RP [1661]. Unmet expectations were more frequently reported by patients with positive surgical margins following surgery; having had a passive role in the decision-making process; and who had higher scores on the decisional conflict scale (i.e., more uncertainty about the treatment decision). Interestingly, positive surgical margins are not directly associated with an increased risk of PC-related mortality [1061]. Active participation and support in the process of forming a preference increases the chance of choosing a treatment that is in line with patients' expectations [1655, 1662-1664].

While it may seem desirable to tailor the patients' role in decision-making to their initial preference, and particularly to a preference for deferring to the advice of the clinician, this does not result in less decisional conflict or regret. Increasing patients' knowledge, regardless of initial preference, may in fact be preferable [1660].

8.3.2.d Decision aids in prostate cancer

Shared decision-making can increase patients' comfort when confronted with management decisions but has been shown to improve health outcome [1665] and additional training appears to be needed for healthcare professionals guiding patients [1666]. Patient education decreased PSA testing [1667] and increased adherence to AS protocols [1668, 1669]. Autonomous active decision-making by patients was associated with less regret after prostatectomy regardless of the method chosen, and decision aids reduce decisional conflict [1670]. Still, guidance is needed to optimise patients' understanding of the options [1671]. Patients prioritised effectiveness and pain control over mode of administration and risk of fatigue when presented with treatment choice in metastasised PCa [1672]. When implementing decision aids, clinical validity and utility should be carefully evaluated and distinguished [1673]. A decision aid should educate as well as promote shared decision-making to optimise efficacy [1674]. Also bear in mind communicative aspects [1675].

8.3.2.e Recommendations for quality of life in men undergoing systemic treatments

Recommendations	Strength rating
Offer males on androgen deprivation therapy (ADT) 12 weeks of supervised (by trained exercise specialists) combined aerobic and resistance exercise.	Strong
Advise males on ADT to maintain a healthy weight and diet, stop smoking, reduce alcohol to ≤ 2 units daily, and have yearly screening for diabetes and hypercholesterolemia. Ensure that calcium and vitamin D meet recommended levels.	Strong
Offer males after any radical treatment specialist nurse-led, multidisciplinary rehabilitation based on the patients' personal goals addressing incontinence, sexuality, depression and fear of recurrence, social support, and positive lifestyle changes.	Strong
Offer males starting on long-term ADT dual emission X-ray absorptiometry (DEXA) scanning to assess bone mineral density.	Strong
Offer anti-resorptive therapy to males on long term ADT with either a BMD T-score of < -2.5 or with an additional clinical risk factor for fracture or when annual bone loss on ADT is confirmed to exceed 5%.	Strong
Measure initial BMD to assess fracture risk in patients on long-term ADT.	Strong

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10. CONFLICT OF INTEREST

All members of the EAU - EANM - ESTRO - ESUR - ISUP – SIOG Prostate Cancer Guidelines Working Group have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer/panel.

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Disclosures: The EAU Guidelines Office certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following:

P. Cornford reported receiving company honoraria or consultation fees from Accord Healthcare, AstraZeneca and Bayer UK; receiving company speaker honoraria fees from Astellas Pharma a/s Danish Sales, AstraZeneca, Bayer UK, Ipsen Biopharm and Janssen Cilag; and serving on the board of trustees of Prostate Cancer Research.

D. Tilki reported receiving company honoraria or consultation fees from A3P Biomedical AB, Astellas Pharma, Bayer Vital, Novartis Pharma and Veracyte.

R.C.N. van den Bergh reported receiving company honoraria or consultation fees from Astellas Pharma International, Ipsen Farmaceutica and Johnson & Johnson Innovative Medicine; participation in a company sponsored speaker's bureau for Amgen; receiving fellowship or travel grants from Bayer; and receiving grants or research support from Astellas and Johnson & Johnson Innovative Medicine.

D. Eberli reported receiving company speaker honoraria fees from Astellas Pharma, Bayer (Schweiz), EDAP Germany and Janssen Cilag; serving as a company consultant to Astellas Pharma, Bayer (Schweiz), EDAP Germany and Iaculis; receiving grants or research support from Astellas Pharma, Bayer (Schweiz) and EDAP TMS; receiving fellowship or travel grants from Bayer (Schweiz); being a stock shareholder in MUVON Therapeutics and Ontrack Biomedical; serving as a director of the Department of Urology at University Hospital Zurich; holding an appointment as a Professor at University of Zurich; and being the owner of three patents.

V. Fonteyne reporting participation in the THUNDER (NCT06282588) and SAVE trials; received honoraria for lectures from Johnson & Johnson, Astellas, Bristol Myers Squibb and Issecam; travel support from Johnson & Johnson; and participation on advisory boards from Astellas.

M. De Santis reported receiving company honoraria or consultation fees from Amgen, Astellas Pharma EMEA, De Santis, AAA, AbVie, Amgen, Astellas, AstraZeneca, Basilea, Bayer, BMS, EISAI, Ferring, Gilead, Immunomedics, Ipsen, Janssen, MSD, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi, SeaGen and Thermosome; and participation in clinical trials by Amgen, Astellas, AstraZeneca, Bayer, BMS, EISAI, Ferring, Ipsen, Janssen, MSD, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi, Amgen, Astellas, AstraZeneca, Bayer, BMS, EISAI, Ferring, Ipsen, Janssen, MSD, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi and SeaGen.

G. Gandaglia reported receiving company speaker honorarium from Accord Healthcare and Ipsen; honoraria or consultation fees from Bayer S.p.A. and Janssen Cilag S.p.A; fellowship, travel grants from Bayer S.p.A. and Ipsen S.p.A; being a company consultant for Telix; and receiving grants/research supports from AIRC - Fondazione AIRC per la ricerca sul cancro.

S. Gillessen reported receiving company honoraria or consultation fees from Amgen, Astellas Pharma, Boehringer Ingelheim Pharma, Daiichi Sankyo Schweiz, Ipsen Innovation, Novartis Pharma, PeerVoice, University of Applied Sciences and Arts of Southern Switzerland, UroPratica Group, EPG Health, Macrogenics, Avalere Health, InnoMedica Schweiz and Silvio Grasso Consulting; receiving company speaker honoraria fees from ASCO, ESMO, Orikata, PlayToKnow, Intellisphere, SGMO and AdMeTech Foundation; receiving fellowship or travel grants from Bayer (Schweiz), Johnson & Johnson Innovative Medicine, Intellisphere and Gilead; serving as a company consultant to Bayer (Schweiz), BMS, Merck - Pfizer Alliance, MSD, Pfizer and LinkinVax; participation in a company sponsored speaker's bureau for SAKK; being the owner of one patent; and attending a senior executive meeting at AstraZeneca.

A.M. Henry reported receiving grants or research support from the University of Leeds; and participation in clinical trials for Cancer Research UK.

J. Oldenburg reported receiving company honoraria or consultation fees from Astellas Pharma Norway, BMS, Janssen Cilag, MSD (Norge), Pfizer and Roche Accord; and receiving company speaker honoraria fees from Astellas Pharma Norway and Janssen Cilag.

D.E. Oprea-Lager reported receiving company honoraria or consultation fees from Novartis, Bayer, Curium, Ipsen, Astellas, Janssen and Telix.

I. van Oort reported receiving grants/research supports from Amgen, Astellas, Bayer B.V. and Novartis Pharma; receiving honoraria or consultation fees from Bayer B.V. and Novartis Pharma; and receiving company speaker honorarium from Recordati B.V.

M. Roberts reported receiving company honoraria or consultation fees from Astellas Pharma Australia, AstraZeneca, Janssen and Cook Medical Australia; receiving fellowship or travel grants from Bayer Australia; receiving grants or research support from ANZUP Cancer Trials Group; serving as a company consultant to BXTAccelyon Australia; and participation in clinical trials by Janssen and AdvanCell Isotopes.

O. Rouvière reported receiving fellowship or travel grants from Philips France; and being the owner of one international patent.

J. Stranne reported being the chair of the Swedish national guidelines committee.

T. Wiegel reported receiving company speaker honoraria fees from Bayer Vital GmbH, Ipsen Pharma GmbH, Janssen, Johnson & Johnson Innovative Medicine, Recordati, Takeda Pharma Vertrieb GmbH & Co. KG; serving as a company consultant to Janssen; serving as a member of the steering committee of the German association of scientific medical societies S3 prostate guidelines.

P. Chiu reported receiving speaker honoraria fees for a lecture.

G. Gandaglia reported receiving company speaker honoraria fees from Accord Healthcare and Ipsen; receiving company honoraria or consultation fees from Bayer and Janssen Cilag; receiving fellowship or travel grants from Bayer and Ipsen; serving as a company consultant to Telix; and receiving grants or research support from AIRC.

E. Linares Espinós reported receiving company honoraria or consultation fees from Bayer, Astellas, Casen Recordati, MSD Spain and Pfizer Spain; receiving company speaker honoraria fees from Johnson & Johnson, Ipsen Pharma, Bayer, and Astellas; serving as a company consultant to Ipsen Pharma, Bayer and Johnson & Johnson; participation in clinical trials by Janssen Cilag; and receiving grants or research support from Astellas.

A. Sachdeva reported receiving company speaker honoraria fees from Ipsen, Janssen Cilag; receiving company honoraria or consultation fees from Ipsen and Veracyte; receiving fellowship or travel grants from the Prostate Cancer Foundation; and participation in the STAMPEDE trial.

G.J.L.H. van Leenders Geert J.L.H. van Leenders is President Elect of the International Society of Urological Pathology (ISUP) and co-chair of the European Society of Pathology (ESP) Uropathology working group.

I.G. Schoots, A. Epure, E. Briers, B. Madsen, A. Farolfi and N. Grivas have nothing to declare.

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