Prostate Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Parker[1], E. Castro[2], K. Fizazi[3], A. Heidenreich[4,] P. Ost[5], G. Procopio[6], B. Tombal[7] & S. Gillessen[8,9], on behalf of the ESMO Guidelines Commitee*

[1]Royal Marsden Hospital, Sutton, UK; [2]Department of Medical Oncology, Virgen de la Victoria University Hospital. Institute of Biomedical Research in Málaga, Malaga, Spain; [3]Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Saclay, Villejuif, France; [4]Department of Urology, Uro-Oncology, Robot-Assisted and Specialized Urologic Surgery, University Hospital of Cologne, Cologne, Germany; [5]Dept of Radiation Oncology, Ghent University Hospital, Ghent, Belgium; [6]Departement of Medical Oncology 1, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; [7]Institut de recherche Clinique, Université catholique de Louvain, Brussels, Belgium; [8]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland and Faculty of Biomedical Sciences, USI, Lugano, Switzerland; [9]Division of Cancer Medicine, University of Manchester, Manchester, UK.

Key words: prostate cancer, surgery, radiotherapy, hormone therapy, chemotherapy

Highlights

• This ESMO Clinical Practice Guideline provides key recommendations on the management of Prostate cancer

• Authorship includes a multidisciplinary group of experts from different institutions and countries in Europe

• Key treatment recommendations are provided

• Recommendations have been updated in the light of new evidence

*_Correspondence to_: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, 6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: February 2020, last update June 2020. This publication supersedes the previously published version—Ann Oncol 2015; 26(suppl. 5): v66-v77.

SCREENING AND EARLY DETECTION

Subclinical prostate cancer is common in men >50 years. Population-based screening of men aged between 55 and 69 years, using prostate-specific antigen (PSA) testing, has been evaluated [1]. After a median follow-up of 16 years, the European screening trial demonstrated a 25% relative reduction in prostate cancer mortality. However, 570 men needed to be invited for screening and 18 patients needed to be treated to prevent one death from prostate cancer, and there was no effect on overall survival (OS).

Risk-adapted early detection of prostate cancer using a baseline PSA has been evaluated in retrospective cohort studies. Men with a PSA >1 ng/mL at 40 years or >2 ng/mL at 60 years are at increased risk of prostate cancer metastasis or death from prostate cancer [2].

Recommendations:

- Population-based PSA screening of men for prostate cancer reduces prostate cancer mortality at the expense of overdiagnosis and overtreatment and is not recommended [I, C]
- Early PSA testing (baseline PSA followed by risk-adapted follow-up) can be offered to men >50 years, men >45 years with a family history of prostate cancer, African-Americans >45 years and *BRCA1/2* carriers >40 years [III, B]
- Testing for prostate cancer in asymptomatic men should not be done in men with a life expectancy <10 years [I, E]

DIAGNOSIS AND PATHOLOGY

The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio and findings on digital rectal examination (DRE) [3]. Physicians are encouraged to use risk calculators incorporating these factors [4]. Multi-parametric magnetic resonance imaging (mpMRI) is recommended before prostate biopsy [5-7]. Targeted transperineal biopsies, in comparison with systematic transrectal biopsies, result in an increased detection rate of clinically significant prostate cancer, a decreased detection rate of clinically insignificant prostate cancer, and fewer adverse events [8]. When mpMRI is positive (i.e. Prostate Imaging–Reporting and Data System [PI-RADS] ≥3), targeted +/- systematic biopsy should be done. When mpMRI is negative (i.e. PI-RADS ≤2), and clinical suspicion of prostate cancer is low, the biopsy can be omitted. Diagnostic work-up is shown in Figure 1.

Recommendations:

- mpMRI should be performed before prostate biopsy [I, B]
- A prostate cancer risk calculator and/or mpMRI should be used to confirm the indication for biopsy in men with elevated PSA [III, C]
- Transperineal biopsies are recommended, rather than transrectal ultrasound (TRUS)-guided biopsies [III, B]
- Each biopsy should be reported individually and evaluated using the ISUP Consensus recommendations [II, B] [9]

STAGING AND RISK ASSESSMENT

Staging and risk assesment are presented in supplementary Tables S1 and S2, available at *Annals of Oncology* online. Patients who are not suitable for treatment with curative intent, by virtue of poor general health, do not normally require staging investigations. Magnetic resonance imaging (MRI) provides T staging [10] and can inform surgical technique with respect to nerve sparing and wide excision of areas of potential extra-prostatic extension). Men with low-risk disease (T1/2, Gleason score [GS] ≤ 6, PSA ≤10) [11] do not require further

imaging. Within the low-risk category, percentage of positive cores, length of core involvement, PSA density and a lower free/total PSA ratio are positively associated with risk of understaging.

Men with intermediate- or high-risk disease [11] should have imaging for nodal or metastatic disease. Whole body MRI, choline-positron emission tomography-computed tomography (PET-CT) [12] and prostate-specific membrane antigen (PSMA)-PET-CT [13,14] have better sensitivity and specificity than CT or bone scan but have not been shown to improve clinical outcomes. The evidence regarding PET and whole body MRI in this setting is not adequate to make a recommendation concerning their use. Patients with localised disease on routine imaging should not be denied radical local treatment solely because metastatic lesions are identified on novel imaging techniques.

Recommendations:

- Localised disease should be classified as low-, intermediate- or high-risk as a guide to prognosis and therapy [III, A]
- Patients with intermediate-risk disease should be staged for metastases using MRI or CT (abdomen and pelvis) and bone scan [III, B]
- Patients with high-risk disease should be staged for metastases using CT (chest abdomen and pelvis) and bone scan [III, B]

MANAGEMENT OF LOCAL/LOCOREGIONAL DISEASE

There is no consensus regarding optimum management of localised disease (Table 1 and Figures 2-3). Patients should be informed of the benefits and harms of the different options. Given the range of treatment options and their side effects, men should be offered the opportunity to consult with both an urologist and a radiation oncologist. Men should be counselled that treatment for prostate cancer may cause sexual dysfunction, infertility, bowel and urinary problems.

Watchful waiting with delayed hormone therapy for symptomatic progression is an option for men who are not suitable for, or unwilling to have, treatment with

curative intent. Active surveillance is a strategy of close monitoring; typically using PSA, repeat biopsies and MRI, keeping curative treatment for those with evidence of disease progression. There is no good evidence comparing different methods of active surveillance [15].

Curative options include radical prostatectomy (RP), external beam radiotherapy (RT), and low-dose-rate brachytherapy. Two randomised controlled trials (RCTs) have compared RP and watchful waiting [16, 17]. The Scandinavian Prostate Cancer Group (SPCG) Study 4 accrued 695 men during the 1990s, at a time when PSA testing was not routinely performed, and may not be applicable to screen-detected cancers. After a mean follow-up of 29 years, the risk of death from prostate cancer was 20.4% and 31.6% in the RP and the watchful waiting groups, respectively. RP increased the rate of erectile dysfunction (80% versus 45%), and urinary leakage (49% versus 21%) [16], but these rates may not be generalisable to high-volume surgical centres.

The PIVOT trial recruited 731 North American men between 1994 and 2002 [17]. They were more representative of men with PSA-detected cancer, but had a remarkably high rate of comorbidity. No significant difference was seen in OS between RP and watchful waiting [hazard ratio (HR) 0.88; 95% confidence interval (CI) 0.71-1.08]. In the low-risk subgroup of 296 men, the risk of death from prostate cancer was <3% at 12 years, with no significant benefit for surgery. Indeed, the trend both in terms of prostate cancer-specific mortality (HR 1.48; 95% CI 0.42-0.54) and overall mortality (HR 1.15; 95% CI 0.80-1.66), favoured watchful waiting rather than surgery. However, the high overall mortality rate of ~50% at 10 years illustrates the recruitment of men with significant comorbidities.

ProtecT is a prospective randomised clinical phase III trial comparing active therapy (RP or RT) versus active monitoring (repeat biopsy in men with a PSA rise of >50% from the baseline value) [18]. The trial recruited 1643 men with localised prostate cancer and after a median follow-up of 10 years there was no statistically significant difference in terms of cancer-specific survival, which was 99% in all three arms. However, there was a statistically significant

increase in the frequency of skeletal metastases and the need for androgen deprivation in the active monitoring arm.

The case for adding radical local treatment for men with high-risk localised and locally advanced disease is based on two RCTs. The SPCG-7 trial included 875 men who received 3 months of combined androgen blockade followed by flutamide monotherapy [19]. They were randomised whether to receive radical RT to the prostate. It showed a beneficial impact of radical RT in terms of cause-specific (11.9% versus 23.9%, $p<0.001$), and overall mortality (29.6% versus 39.4%, $p=0.004$). The National Cancer Institute of Canada/Medical Research Council (NCIC/MRC) trial randomised high-risk patients to either lifelong androgen deprivation therapy (ADT) alone or to ADT plus RT. The addition of RT improved the 7-year survival from 66% to 74% ($p=0.003$) [20].
For patients receiving radical prostate RT, dose escalation using intensity-modulated RT or image-guided RT improves biochemical control with acceptable toxicity [21]. Moderate hypofractionation is non-inferior in terms of biochemical control, is more convenient and has acceptable toxicity [22].
Patients treated with RP for high-risk disease often require post-operative RT +/- ADT.

Recommendations

- Watchful waiting with delayed ADT for symptomatic progression is an option for men who are not suitable for, or unwilling to have, radical treatment [I, A]
- Active surveillance is recommended for men with low-risk disease [II, A]
- RP or RT (external beam or brachytherapy) are options for men with low-risk disease not suitable for active surveillance [III, B]
- RP or RT (external beam or brachytherapy) are recommended for men with intermediate-risk disease [I, B]
- Primary ADT alone is not recommended as standard initial treatment for non-metastatic disease [I, D]
- External beam RT plus ADT is recommended for men with high-risk or locally advanced prostate cancer [I, B]

- RP plus pelvic lymphadenectomy is an option for selected men with high-risk disease [III, B]

Neo-adjuvant and adjuvant hormone treatment

The value of neo-adjuvant and concurrent ADT, with RT, in men with high-risk localised and locally advanced disease, has been established by multiple randomised trials. For example, in the Trans Tasman Radiation Oncology Group (TROG) 96-01 trial, 818 men with locally advanced prostate cancer were randomly assigned to RT alone, RT plus 3 months neo-adjuvant and concurrent combined androgen blockade (CAB) or RT plus 6 months CAB [23]. Compared with RT alone, the use of 6 months hormone therapy significantly improved overall mortality (HR 0.63; 95% CI 0.48-0.83). Similarly, the Radiation Therapy Oncology Group (RTOG) trial 8610, in 456 men with T2-4 disease, found an improvement in 10-year prostate cancer-specific mortality (23% versus 36%; *p*=0.01) for the addition of 4 months neoadjuvant and concurrent ADT [24].

Intermediate-risk localised prostate cancer has been subdivided into favourable and unfavourable categories [25]. Unfavourable intermediate-risk disease was defined as any of primary Gleason pattern 4, percentage of positive biopsy cores ≥50%, or ≥2 intermediate-risk factors (cT2b-c, GS 7, PSA 10-20). Patients with unfavourable intermediate-risk disease have a worse outcome than those with favourable intermediate-risk disease, and might be more likely to benefit from neoadjuvant ADT.

Adjuvant ADT, after RT, has been studied in multiple RCTs. The RTOG 92-02 trial randomised 1554 patients to receive either 4 months or 28 months of ADT in addition to RT [26]. In an unplanned subgroup analysis, the addition of adjuvant ADT improved OS in those with a GS of 8-10 (81.0% versus 70.7%, *p*=0.044). The European Organisation for Research and Treatment of Cancer (EORTC) 22961 trial randomised 970 men with locally advanced disease to receive either 6 months or 36 months of ADT in addition to radical RT [27]. The

5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively (HR: 1.42; CI: 1.09-1.85).

A recent RCT evaluated 18 versus 36 months adjuvant ADT in 630 men with high-risk prostate cancer [28]. After a median follow-up of 9.4 years, the 5-year OS was 91% for the 36-months arm and 86% for the 18-months arm (*p*=0.07). While this was a relatively small trial, with a more favourable case mix than EORTC 22961, given the additional toxicity of longer-term ADT, 18-months treatment may be preferred by some patients.

No large RCTs are available for adjuvant treatment following RP for lymph node-positive disease. Based on the data of a large retrospective series including 2596 patients with pN1 disease, combined adjuvant RT and 2-years ADT results in an improved 8-year cancer-specific mortality rate for men with two positive lymph nodes associated with pT3b/pT4 and/or positive surgical margins as compared to RT alone [29]. However, the option of PSA-triggered follow-up and initiation of ADT at time of PSA rise was not included.

Recommendations:

- Men receiving radical RT for intermediate-risk disease should have short course ADT for 4-6 months [I, A]

- Men receiving radical RT for high-risk disease should have long course ADT (18-36 months) [I, A]

Neoadjuvant docetaxel for M0 disease

Six RCTs have tested early docetaxel-based chemotherapy in high-risk localised disease. GETUG-12 compared standard of care (ADT for 3 years plus RT) with or without 4 cycles of docetaxel-estramustine. The primary endpoint of relapse-free survival (RFS) was improved (HR: 0.71; 95% CI: 0.54-0.94, *p*=0.017) [30]. A recent update with a median follow-up of 12 years showed that clinical RFS (cRFS; defined as metastases, local relapse or death) was also improved with docetaxel (median cRFS 13.9 years versus 12.5 years; HR 0.75; 95% CI 0.56-1.00; *p* 0.0491) [31]. RTOG 0521 tested RT plus 2 years ADT with

or without 6 cycles of docetaxel and reported a borderline improved RFS [HR: 0.76; (95% CI: 0.57-1.00); *p*=0.05]. OS did not reach significance by standard 2-sided *p* value (1-sided *p*=0.03; HR 0.68; 95% CI 0.44-1.03) [32]. A subset of men randomised in the STAMPEDE trial had high-risk localised disease (and/or pelvic enlarged lymph nodes) and RFS was improved in men randomised to receive docetaxel (HR 0.60; 95% CI 0.45-0.80; $p=0.283x10^{-3}$) [33]. A meta-analysis of these three trials supported RFS improvement with docetaxel in men with high-risk localised disease (HR 0.70; 95% CI 0.61-0.81; *p*<0.0001) but OS data were immature [34].

Since then, three other trials [SPCG-12, SPCG-13 and VA Cooperative Study Program (CSP) #553] have reported preliminary data in congresses with no significant RFS benefit [35-37]. SPCG-13 may have included patients at insufficient risk of relapse to derive any benefit [35]. SPCG-12 did not use ADT as part of the standard of care [36], and VA CSP #553 had limited power (only 297 patients participated), although a trend favouring docetaxel was observed [37].

In men with high-risk localised prostate cancer, very long-term follow-up is needed to show survival differences: assuming cooperative groups are able to collect long-term data, this should be achieved around 2020-2025 for these trials. Based on the available data, offering docetaxel-based chemotherapy may be a reasonable option for younger, fit men with multiple risk factors for recurrence.

Recommendation

- Neoadjuvant docetaxel chemotherapy may be offered prior to RT for young, fit men with very high-risk localised prostate cancer [I, C]

Post-operative RT

Post-operative RT following RP may be given as adjuvant RT (ART; undetectable postoperative PSA) or salvage RT (SRT; persistent or rising PSA). Three RCTs investigated ART compared with observation (EORTC

22911, SWOG 8794 and ARO 96-02) [38]. All showed improved biochemical control for ART, but no consistent OS benefit was seen. More recent trials, RADICALS-RT, RAVES and GETUG-17, have compared ART with a policy of observation with early SRT given at the time of PSA failure. All three trials have been combined in the ARTISTIC meta-analysis that was presented at ESMO 2019. The results show that ART has some harms (increased bladder and bowel morbidity), but no proven benefit in terms of biochemical PFS. Thus, observation with SRT in the event of PSA failure is the current standard after radical prostatectomy. SRT should be given early. Outcomes are more favourable if SRT is used when PSA is <0.5 ng/ml [39].

Three trials have compared SRT versus SRT plus 6 months of ADT (GETUG-AFU 16, RTOG 0534) or plus 24 months of bicalutamide (RTOG 9601) [40]. RTOG 9601 showed a a reduced rate of prostate cancer death (HR 0.77; 95% CI 0.59-0.99; *p*=0.04) and improved OS (HR 0.49; 95% CI 0.32-0.74; *p*<0.001) [40]. *Post hoc* subgroup analysis indicated that men with a pre-SRT PSA above 0.7 ng/ml, GS 8-10 and positive margins had the largest benefit from the addition of bicalutamide [40]. The GETUG-AFU 16 trial showed an improvement in metastasis-free survival (HR: 0.73; 95% CI: 0.54-0.98; *p*=0.034) [41], but not OS.

The SPPORT-trial, presented at the 2018 American Society for Radiation Oncology (ASTRO) annual meeting [42] investigated the potential of pelvic nodal RT with 6 months of ADT as compared with prostate bed-only RT or prostate bed RT plus 6 months of ADT. The addition of pelvic RT improved freedom from failure, as well as an improvement in freedom from metastases for the comparison with prostate bed-only RT (HR 0.52; 95% CI 0.30-0.92; *p*=0.014). There were no OS differences observed between arms.

Recommendations

- Following RP, patients should have their serum PSA level monitored, with salvage RT recommended in the event of PSA failure [III, B]
- Adjuvant post-operative RT after RP is not routinely recommended [I, B]

- Salvage RT should start early (e.g. PSA <0.5 ng/mL) [III, B]Concomitant ADT for 6 months or bicalutamide 150 mg daily for 2 years may be offered to men having salvage RT [I, B]
- Men having SRT to the prostate bed may be offered pelvic nodal RT [I, C]

Treatment of relapse after radical local treatment

Re-staging

For patients with biochemically recurrent prostate cancer, PSMA-PET imaging is replacing conventional imaging, based on its superior sensitivity and specificity [43]. Nevertheless, there are no trials indicating that the earlier detection of recurrence and subsequent change in management improves outcomes. The study of modern imaging methods has focused on their diagnostic performance, not their effect on care pathways [43].

Local salvage therapy

The natural history of PSA recurrence following primary treatment [44] is long, and life expectancy should be taken into account when considering local treatment options. Molecular imaging studies have indicated that up to 50% of men experience a local recurrence in case of a PSA rise [43]. mpMRI is useful in the detection of local recurrence and can guide targeted biopsies. In case of a biopsy-confirmed local recurrence and the absence of metastases, several local treatment options are available, such as salvage RP, high-intensity focused ultrasound, cryoablation or brachytherapy. Taken together, these treatments typically give only temporary biochemical control in most patients with important morbidity [45]. None of these options have been compared head-to-head.

Metastasis-directed therapy

Earlier visualisation of recurrence makes it technically possible to selectively ablate metastases. Hypothetically, this would slow down progression and improve survival [46]. Most evidence in this setting comes from retrospective case series [47]. More recently, two randomised phase II trials have been published [48, 49]. The STOMP trial showed an improved biochemical progression and time to palliative ADT with metastasis-directed therapy

compared with observation and deferred ADT [49]. In the SABR-COMET trial, different solid tumour types were included, of which 16% were prostate cancer. This trial showed improved OS for additional stereotactic body RT (SBRT) to standard of care [49]. Both trials have paved the way for larger confirmatory phase III trials, but should not be considered as conclusive evidence to offer metastasis-directed therapy.

Systemic therapy

Two randomised trials, TOAD and ELAAT, have compared early versus deferred ADT for men with a PSA failure after local therapy [50]. The reasons to start ADT were development of symptoms or metastases on conventional imaging or PSA doubling time decreasing to ≤6 months. Pooled analysis found no survival benefit with early ADT (HR 0.75; 95% CI 0.40-1.41; *p*=0.37) [51]. Early ADT had an adverse effect on quality of life (QoL), specifically in terms of sexual activity and hot flushes [50].

Intermittent versus continuous ADT was studied in a randomised trial of 1386 patients with a PSA at relapse of >3.0 ng/mL >1 year after radical RT. Intermittent ADT had a more favourable toxicity profile with no difference in OS (HR 1.02; 95% CI 0.86-1.21) [52].

Recommendations

- Men with biochemical relapse after radical RT who may be candidates for local salvage or metastasis-directed treatment should undergo imaging with PET-CT [III, B]
- Early ADT alone is not recommended for men with biochemical relapse unless they have a rapid PSA doubling time, symptomatic local disease or proven metastases [II, D]
- Men starting ADT for biochemical relapse, in the absence of metastatic disease, should be offered intermittent rather than continuous treatment [I, B]

HORMONE-NAIVE METASTATIC PROSTATE CANCER

Treatment recommendations for hormone-naive metastatic prostate cancer are shown in Figure 4. Addition of abiraterone, apalutamide, enzalutamide or docetaxel to ADT improves OS in metastatic hormone-naive prostate cancer (mHNPC). Most of the relevant trials, discussed below, largely included men with *de novo* metastatic disease, and caution should be used when extrapolating the results to men who relapsed with metastases after previous local treatment.

The benefit of docetaxel for mHNPC was established by two phase III trials, CHAARTED [53] and STAMPEDE [33]. The CHAARTED study randomised 790 patients to receive ADT alone or in combination with docetaxel 75 mg/m^2 every 21 days for 6 cycles. Docetaxel improved OS (HR 0.72; 95% CI 0.59-0.89). The STAMPEDE study is a multi-arm, multi-stage phase III study designed to test whether the addition of various treatments to ADT improves OS. It includes patients with both M0 and M1 disease. Patients were randomised to ADT alone (n=1184) or in combination with docetaxel 75 mg/m^2 every 21 days with prednisone 10 mg daily for 6 cycles (n=592). The addition of docetaxel in M1 patients significantly improved OS compared with ADT alone (HR 0.76; 95% CI 0.62-0.92). The OS benefit for docetaxel was similar when combined with zoledronic acid (HR 0.79; 95% CI 0.66-0.96). A third study, GETUG-AFU 15 [54] randomised 385 mHNPC patients to receive ADT or ADT plus docetaxel 75 mg/m^2 every 21 days for 9 cycles. Patients in the chemotherapy arm had improved PSA progression-free survival (PFS) and radiographic PFS (rPFS), but these did not translate into a benefit in OS (HR 1.01; 95% CI 0.75-1.36). Subgroup analysis of the CHAARTED study showed more pronounced benefit in patients with high-volume disease (HR 0.63; 95% CI 0.50-0.79) [55], defined as the presence of $\geq$4 bone metastases with $\geq$1 beyond vertebral bodies and pelvis, visceral metastasis or both. However, meta-analysis of CHAARTED, STAMPEDE and GETUG-AFU 15 have confirmed the improvement in OS with the addition of docetaxel to ADT regardless of disease volume (HR 0.77; 95% CI 0.68-0.87) [34, 56].

The addition of abiraterone to ADT has demonstrated improved OS compared with ADT alone in two phase III trials, LATITUDE [57] and STAMPEDE [58]. Both studies randomised participants to ADT alone or in combination with abiraterone 1000 mg plus prednisone 5 mg daily until disease progression. LATITUDE randomised 1199 patients with high-risk metastatic prostate cancer, defined as the presence of at least two of the following: GS ≥8, ≥3 bone metastases or visceral metastases. The addition of abiraterone to ADT resulted in a significant improvement in OS (HR 0.62; 95% CI 0.51-0.76) [57]. Updated data after crossover and 2-year additional follow-up confirmed this (HR 0.66; 95% CI 0.56-0.78) [59]. A similar benefit in survival was observed in the STAMPEDE trial for the M1 subgroup (HR 0.63; 95% CI 0.52-0.76) [58]. LATITUDE enrolled only patients with *de novo* metastatic prostate cancer, and only 5% of patients included in STAMPEDE were relapsing M1. Therefore, the benefit of adding abiraterone to ADT in the latter group of patients is uncertain.

The phase III trial TITAN demonstrated that addition of apalutamide to ADT improves OS in mHNPC [60]. The study randomised 1052 participants to ADT alone or in combination with apalutamide 240 mg per day. A total of 16% of patients had received treatment for localised disease and were enrolled at M1 relapse. Only 11% of patients had recevied early docetaxel. Most patients had high-volume disease (63%). The addition of apalutamide improved OS (HR 0.67; 95% CI 0.51-0.89; p=0.005) with no significant differences according to disease volume. Given the limited number of patients that received apalutamide after docetaxel, the benefit of this strategy remains unclear.

The benefit of adding enzalutamide to ADT for the treatment of mHNPC patients has been established by two phase III studies, ARCHES [61] and ENZAMET [62]. ARCHES randomised 1150 mHNPC patients to ADT plus enzalutamide 160 mg daily or ADT plus placebo. Participants were stratified by disease volume and prior docetaxel therapy. At the interim analysis, the primary endpoint was met, as enzalutmide significantly improved rPFS [HR: 0.39; 95% CI: 0.30-0.50; p<0.001]. The rPFS benefit was consistent across all prespecified subgroups, including disease volume and prior docetaxel

chemotherapy. At the time of this interim analyses, data on OS were immature. The second phase III study, ENZAMET [62], randomised 1125 men with mHNPC to either ADT plus other NSAAs, including bicalutamide, nilutamide or flutamide, versus ADT plus enzalutamide. Enzalutamide resulted in a significant improvement in OS (HR 0.67; 95% CI 0.52-0.86). This is the first study to examine the use of an androgen receptor (AR) signalling inhibitor with or without concurrent docetaxel; 45% of patients were planned to receive docetaxel. The HR for OS was 0.53 (95% CI 0.37-0.75) for those who were not planned to receive docetaxel, and 0.90 (95% CI 0.62-1.31) for those who were planned to receive docetaxel.

Docetaxel plus ADT and abiraterone plus ADT have been compared in an opportunistic randomised analysis from the STAMPEDE trial, suggesting similar outcomes in the M1 subgroup [63]. On the other hand, indirect Bayesian comparisons have suggested that the survival and QoL benefit provided by abiraterone may be greater than that seen with docetaxel [64]. Since no biomarkers have been identified to select one therapy over another, the decision to use abiraterone, apalutamide, enzalutamide or docetaxel should be individualised taking into consideration of cost, access to treatment, toxicity profiles, duration of treatment, comorbidities and patient preferences.

Two randomised trials, HORRAD [65] and STAMPEDE [66], have compared lifelong ADT alone or in combination with RT to the primary tumour for mHNPC. The HORRAD trial randomised 446 patients to receive ADT alone or in combination with RT to the primary (70 Gy in 35 fractions for 7 weeks or 57.76 Gy in 19 fractions for 6 weeks). RT improved time to PSA progression (HR 0.78; 95% CI 0.63-0.97), but not OS (HR 0.90; 95% CI 0.70-1.14) [65]. The STAMPEDE trial allowed docetaxel in both arms in addition to ADT. RT to the primary was then commenced within 3-4 weeks after the last docetaxel dose (55 Gy in 20 fractions over 4 weeks or 36 Gy in 6 fractions over 6 weeks). RT improved failure-free survival (HR 0.76; 95% CI 0.68-0.84; $p<0.0001$) but not OS (HR 0.92; 95% CI 0.80-1.06). The pre-specified low-volume subgroup, defined according to the CHAARTED criteria, had a significant benefit in both

failure-free survival (HR 0.59; 95% CI 0.49-0.72) and OS (HR 0.68; 95% CI 0.52-0.90).

Management of bone health and prevention of cancer treatment-induced bone loss (CTIBL) is an important part of the treatment of men prostate cancer under homonal tretament. Prevention of CTIBL is covered by a separate ESMO guidelines [67] .

Recommendations

- ADT is recommended as first-line treatment for mHNPC in combination with abiraterone/prednisone [ESMO-MCBS v1.1 score: 3] or apalutamide [ESMO-MCBS v1.1 score: 3] or docetaxel [ESMO-MCBS v1.1 score: 4] or enzalutamide [ESMO-MCBS v1.1 score: 3] [I, A]
- RT to the primary tumour combined with the systemic treatment is recommended for patients with low-volume mHNPC [I, A]
- ADT alone is recommended as first-line systemic treatment for mHNPC in men who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel [III, A]
- For men starting on ADT, management to prevent CTIBL is recommended [67]

NON-METASTATIC CASTRATE-RESISTANT PROSTATE CANCER

Castrate-resistant prostate cancer (CRPC) is defined as disease progression during ADT, with serum testosterone at castrate levels [68]. The absence of metastases (M0) on traditional imaging (bone scintigraphy and CT scan) has been used to identify M0 CRPC disease [68]. This disease setting exists because of the use of early, long-term ADT for men with non-metastatic prostate cancer. If ADT is delayed in men with biochemical failure after radical treatment until the site of recurrence is detected, M0 CRPC will be unusual because men will typically only develop castrate-resistant disease after the detection of metastases.

Apalutamide significantly increased median metastasis-free survival (40.5 months versus 16.2 months, HR 0.28; 95% CI 0.23-0.35) and time to symptomatic progression (HR 0.45; 95% CI 0.32-0.63) as compared with placebo in a multicentre, randomised, placebo-controlled, phase III trial (SPARTAN) conducted in 1207 men with high-risk M0 CRPC (baseline PSA >2.0 ng/ml and a PSA doubling time of ≤10 months). Data on OS is still immature (HR 0.70; 95% CI 0.47-1.04). The most frequent side effects observed in the experimental arm were rash, hypertension, fracture, hypothyroidism and mental-impairment disorder [69].

Enzalutamide was evaluated in patients with high-risk M0 CRPC (PROSPER Trial). In 1401 patients, enzalutamide was superior to placebo with regard to the primary endpoint of median metastasis-free survival (36.6 months versus 14.7 months, HR 0.29; 95% CI 0.24-0.35), and the key secondary endpoints of median time to PSA progression (37.2 versus 3.9 months; HR 0.07; 95% CI 0.05-0.08) and time to subsequent antineoplastic therapy (39.6 versus 17.7 months; HR 0.21; 95% CI 0.17-0.26). Data on OS is still immature. Side effects most commonly reported in the enzalutamide group were fatigue, hypertension, adverse cardiovascular events and mental-impairment disorders [70].

Darolutamide was evaluated in the ARAMIS trial, a multicentre, randomised, double-blind, placebo-controlled, phase III trial involving 1509 men with high-risk M0 CRPC and a PSA doubling time of ≤10 months. Darolutamide significantly increased the median metastasis-free survival compared with placebo (median 40.4 months versus 18.4 months; HR 0.41; 95% CI 0.34-0.50). Data on OS is immature. Grade 3 or 4 adverse events were reported in 19.5% versus 24.7% of patients receiving placebo and darolutamide, respectively [71].

Recommendation

- Apalutamide [ESMO-MCBS v1.1 score: 3], darolutamide [ESMO-MCBS v1.1 score: 3] or enzalutamide [ESMO-MCBS v1.1 score: 3] should be considered as options for men with M0 (on bone scan and CT) CRPC and a high risk of disease progression [I, B]

METASTATIC CRPC

For men with metastatic CRPC (mCRPC), both bicalutamide and low-dose corticosteroids show a benefit in terms of PSA and symptomatic responses, but no randomised trials have demonstrated a benefit in OS [72, 73].

The combination of abiraterone acetate and prednisone was compared with placebo plus prednisone in the COU-AA-302 trial [74] in >1000 men with chemotherapy-naive, asymptomatic or mildly symptomatic mCRPC. Abiraterone significantly improved OS (HR 0.79; 95% CI 0.66-0.95). The main specific side effects were hypokalaemia, hypertension, oedema and cardiac events. Low-dose abiraterone taken with food appeared to have similar activity to standard dose abiraterone under fasting conditions [75]; however, this has not been tested in phase III trials.

In the same setting, 1717 patients were treated with enzalutamide or placebo in the PREVAIL trial [76]. Enzalutamide was superior to placebo in terms of OS (HR 0.71; 95% CI 0.60-0.84), with fatigue/asthenia and hypertension as the most common adverse events.

The role of chemotherapy in mCRPC was established in two phase III randomised trials. In the TAX-327 trial, in a population of 1006 patients with mCRPC, docetaxel (75 mg/m^2 three-weekly) combined with prednisone significantly increased OS as compared with mitoxatrone plus prednisone (HR 0.76; 95% CI 0.62-0.94) [77]. Similarly, the SWOG-9916 trial showed that the combination of docetaxel (60 mg/m^2 three-weekly), extramustine and prednisone was superior to mitoxantrone plus prednisone in prolonging OS (HR 0.8; 95% CI 0.67-0.97). In both studies, docetaxel increased the risk of myelosuppression, febrile neutropaenia, fatigue, alopecia, diarrhoea, neuropathy and peripheral oedema [78].

The ALSYMPCA trial showed that the treatment with radium-223 (^{223}Ra), a bone-targeted alpha-emitter, significantly increased OS (HR 0.70; 95% CI 0.58-0.83) and time to first symptomatic skeletal event (HR 0.66; 95% CI 0.52-0.83)

compared with placebo in 926 patients with progressive bone-predominant, symptomatic, mCRPC [79]. Side-effects of ^{223}Ra include thrombocytopaenia (3% G3) and diarrhoea (2% G3). Based on this trial, ^{223}Ra was rated at the highest level of the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) [80]. However, the ERA-223 trial showed an increased incidence of fractures (28.6% versus 11.4%), among patients receiving ^{223}Ra in combination with abiraterone acetate plus prednisone compared with patients receiving placebo in combination with abiraterone acetate plus prednisone [81]. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has restricted the use of ^{223}Ra to patients who have received at least two lines of systemic treatment for CRPC (abiraterone/enzalutamide and docetaxel) or who are ineligible to receive these therapies [82]. The administration of ^{223}Ra in association with abiraterone acetate and prednisone/prednisolone is not permitted.

In the post-docetaxel setting, cabazitaxel improved OS (HR 0.70; 95% CI 0.59-0.83) compared with mitoxantrone in 755 patients (TROPIC trial) [83]. The treatment was associated with increased myelosuppression, including febrile neutropaenia and diarrhoea. Similarly, abiraterone plus prednisone, tested against placebo plus prednisone in the COU-301 study [84] improved OS (HR 0.74; 95% CI 0.64-0.86). Enzalutamide was tested against placebo in the post-docetaxel setting in the AFFIRM trial, and also improved OS (HR 0.63; 95% CI 0.53-0.75) [85].

The optimal sequence or combination of all these agents is largely unknown. There is strong evidence suggesting cross-resistance between abiraterone and enzalutamide. A second AR inhibitor (abiraterone for those with prior enzalutamide and vice versa) had only modest activity [86] .The CARD trial compared cabazitaxel versus a second AR inhibitor. The median OS was 13.6 months with cabazitaxel and 11.0 months with the second androgen-signaling-targeted inhibitor (HR 0.64; 95% CI, 0.46 to 0.89; P = 0.008). In the control arm, the response rate and the duration of response to a second AR-inhibitor was poor [87].

In daily practice, sequencing decisions will be made in light of the distribution, extent and pace of disease, comorbidities, previous treatments (chemotherapy or new hormone agents), patient preferences and drug availability.

Recommendations

- Abiraterone or enzalutamide [ESMO-MCBS v1.1 scores: 4] are recommended for asymptomatic/mildly symptomatic men with chemotherapy-naive mCRPC [I, A]

- Docetaxel [ESMO-MCBS v1.1 score: 4] is recommended for men with mCRPC [I, A]

- In patients with mCRPC in the post-docetaxel setting, abiraterone, enzalutamide and cabazitaxel [ESMO-MCBS v1.1 score: 3] are recommended options [I, A]

- In patients with bone metastases from CRPC at risk for clinically significant SREs, a bisphosphonate or denosumab are recommended (see section on palliative care) [I, B]

- ^{223}Ra [ESMO-MCBS v1.1 score: 5] is recommended for men with bone-predominant, symptomatic mCRPC without visceral metastases [I, B]

- ^{223}Ra is not recommended in combination with abiraterone and prednisolone [I, E]

- The use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended [II,B]

PRECISION MEDICINE

Various tissue-based molecular assays provide prognostic information, additional to conventional clinico-pathological parameters, regarding outcomes of conservative management and the likelihood of relapse following treatment

of the primary [88, 89]. Assessment of their clinical utility would require long-term prospective studies, and cost-effectiveness analyses.

AR splice variant 7 (AR-V7) detected in circulating tumour cells is prognostic in CRPC [90]. AR-V7-positive patients are less likely to respond to abiraterone and enzalutamide than AR-V7-negative patients [91], whilst AR-V7 status does not seem to affect the response to taxanes [85]. Prevalence of AR-V7 is low prior to treatment but increases with subsequent therapy lines [85]. Thus, it would be of little use to investigate AR-V7 status in the treatment-naïve setting. Switching from one AR signalling inhibitor to another after disease progression is rarely effective, and a therapy with a different mechanism of action (i.e. taxane) would be preferable. Therefore, AR-V7 is of limited value for therapy selection and cannot be recommended.

Actionable targets are identified in the majority of advanced prostate tumours [92]. Approximately 20% of metastatic prostate cancers harbour aberrations in genes involved in DNA damage and repair (DDR) and *BRCA2* is the most commonly altered [92]. A substantial proportion of these aberrations are also present in the germline [92]. Prostate tumours related to germline *BRCA2* mutations often have GS ≥8, nodal and distant metastases at diagnosis, but these genetic variants cannot be excluded in patients without such clinico-pathological features [93]. Germline mutations in *BRCA2* have been associated with poor clinical outcomes across different disease states [93] whilst the prognostic implications of inheritable mutations in other DDR genes are less well established. Importantly, 30% of metastatic prostate cancer patients found to carry a germline DDR mutation did not have a previous family history of cancer [94]. Due to the prevalence of germline DDR in advanced prostate cancer (12%-16%) [93], these patients should be offered germline screening regardless of tumour features at diagnosis or family history of cancer. Men with localised prostate cancer should also be considered for germline testing if at least two close blood relatives on the same side of the family have been diagnosed with tumours linked to hereditary cancer predisposition syndromes (including breast, ovarian, prostate, pancreatic, melanoma, sarcoma,

adrenocortical, brain, colorectal, endometrial, gastric, thyroid and kidney cancers) [95]. The germline origin of pathogenic mutations affecting cancer-risk genes identified by tumour sequencing should also be investigated [96]. There is limited evidence to guide prostate cancer management based on germline status, but early identification of mutation carriers may contribute to the prevention and early diagnosis of tumours in relatives.

Some germline and somatic mutations in genes involved in the homologous recombination pathway, including *BRCA2*, are potential predictors of response to platinum-based chemotherapy and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors [97]. Tumours with germline and somatic mismatch repair defects are likely to respond to pembrolizumab [98, 99].

The PROFOUND trial tested olaparib versus a second AR axis inhibitor in patients with mCRPC with alterations in any of 15 genes with a role in DDR whose disease had progressed on prior new hormonal agent therapy. In 245 patients who had at least one alteration in *BRCA1*, *BRCA2*, or *ATM*, olaparib improved rPFS (HR 0.34 (0.25-0.47) and OS (HR 0.64 (0.43-0.97) [100]. In the control arm, the response rate and the duration of response to a second AR axis inhibitor was poor.

Recommendations

- Tissue-based molecular assays may be used in conjunction with clinico-pathological factors for treatment decision making in localised prostate cancer [IV, C]
- Germline testing for *BRCA2* and other DDR genes associated with cancer predisposition syndromes is recommended in patients with family history of cancer and should be considered in all patients with metastatic prostate cancer [III, B]
- Consider tumour testing for homologous recombination genes and mismatch repair defects (or microsatellite instability) in patients with mCRPC [II, B]

- Patients with pathogenic mutations in cancer-risk genes identified through tumour testing should be referred for germline testing and genetic counselling [IV, A]
- Olaparib can be considered after new hormonal agents for patients with mCRPC with alteration in *BRCA1* or *BRCA2* [1, B]

PALLIATIVE CARE

Fractionated versus single-fraction RT for bone pain has been compared in multiple randomised trials. Single-fraction treatment provides similar pain relief [101]. A recent non-inferiority phase II trial indicated that the single-fraction dose of 14-16 Gy using SBRT results in a better pain response than multifraction RT [102]. Multifraction RT is commonly used for bone metastatic disease associated with complications such as nerve root compression from soft tissue extension.

Zoledronic acid, a bisphosphonate, was shown to prolong time to first skeletal-related event (SRE), namely fracture, spinal cord compression, surgery or RT for bone pain or a change in anticancer treatment for bone pain [103]. However, there was no difference in disease progression, OS or QoL. Adverse effects included anaemia, fever, myalgia and osteonecrosis of the jaw (ONJ). Denosumab, a RANK ligand inhibitor, has been compared with zoledronic acid [104]. Denosumab was superior with respect to time to first SRE (HR 0.82; 95% CI 0.71-0.95, p=0.0002), but was associated with an increased risk of hypocalcaemia (13% versus 6%) and a trend towards higher incidence of ONJ (2.3% versus 1.3%). There was no difference in OS.

The management of mCRPC has changed markedly since the trials of zoledronic acid and denosumab were done. Abiraterone, enzalutamide, corticosteroids and ^{223}Ra all increase the risk of fragility fractures but reduce the risk of other SREs. These changes have heightened awareness of the importance of bone health (see below) in men on ADT. If the bone health

recommendations are followed, the added value of zoledronic acid or denosumab for SRE prevention is unclear.

Spinal cord compression is a devastating complication of metastatic prostate cancer and early detection is critical for successful management. A systematic review found that spinal cord compression is a common finding, even in asymptomatic patients with metastatic prostate cancer and spinal metastases [51].

Beta-emitting, bone seeking radionuclides such as strontium-89 and samarium-153 hydroxyethylidene diphosphonate (^{89}Sr-HEDP and ^{153}Sm-HEDP) have proven symptomatic benefits in the treatment of mCRPC. However, their use is limited by myelotoxicity and they have largely been superseded by ^{223}Ra.

Recommendations

- A single fraction of external beam RT is recommended for palliation of painful, uncomplicated bone metastasis [I, A]
- In patients with bone metastases from CRPC at risk for clinically significant SREs, a bisphosphonate or denosumab are recommended [I, B]
- MRI of the spine to detect subclinical cord compression is recommended in men with CRPC with vertebral metastases [III, B]
- Urgent MRI of the spine to detect cord compression is very strongly recommended in men with CRPC with vertebral metastases and neurological symptoms [III, A]

FOLLOW-UP AND LONG-TERM IMPLICATIONS

ADT may cause hot flushes, lethargy, mood changes, osteoporosis, insulin resistance and muscle loss. Because survival in mCRPC has improved substantially, men are living longer on ADT. Taken together with the adverse effects on bone health of abiraterone, enzalutamide, steroids and ^{223}Ra, bone health in men with prostate cancer is an increasingly important issue.

The FRAX® (Fracture Risk Assessment Tool) score to estimate the risk of fragility fracture is not directly applicable to such men because it does not include a correction specifically for use of ADT. The risk of fragility fracture in men on long-term ADT exceeds accepted intervention thresholds. Even prior to starting ADT, a large proportion of men diagnosed with prostate cancer have osteopaenia or osteoporosis [105].

Lifestyle measures (weight-bearing exercise, stopping smoking, ≤2 units of alcohol daily and adequate calcium intake and vitamin D status) help to maintain bone health. Treatment with an oral bisphosphonate, such as alendronic acid, reduces the incidence of fractures [106]. Alendronic acid should be taken after an overnight fast, at least 30 minutes before food, drink or other medicines. Whole tablets should be swallowed with a glass of water. Patients should remain upright for 30 minutes. If an oral bisphosphonate is not tolerated, zoledronic acid every 12 months or denosumab every 6 months are appropriate alternatives.

Recommendations

- Lifestyle measures to maintain bone health are recommended for men on ADT: weight-bearing exercise, stopping smoking, ≤2 units alcohol daily, adequate calcium intake and vitamin D status (reach and maintain reference vitamin D levels) [IV, B]
- Men starting long-term ADT should:
    - either be offered an oral bisphosphonate [I, B]
    - or be monitored with DEXA scanning and then treated according to the guidelines for CTIBL [67] [IV, B]

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors.

An ESMO-MCBS table with ESMO-MCBS scores is included in supplementary Table S3, available at *Annals of Oncology* online. ESMO-MCBS v1.1 [107] was used to calculate scores for new therapies/indications approved by the EMA since 1 January 2016 (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. Levels of evidence and grades of recommendation have been applied using the system shown in supplementary Table S4, available at *Annals of Oncology* online [108]. Statements without grading were considered justified standad clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

ACKNOWLEDGEMENTS

The ESMO Guidelines Committee would like to thank the ESMO Faculty and other experts who provided critical reviews of these ESMO Clinical Practice Guidelines.

FUNDING

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

DISCLOSURE

CP has reported honoraria from Bayer, Janssen and Advanced Accelerator Applications (AAA) and research grants from Bayer; EC has reported honoraria from Astellas, AstraZeneca, Bayer, Janssen and Pfizer and research grants from AstraZeneca, Bayer and Janssen; KF has reported participation to advisory boards/honoraria for Astellas, AAA, Bayer, Clovis, Curevac, Incyte, Janssen, Merck Sharp & Dohme, Orion, Sanofi; AH has reported paid consultancy for Amgen, Astellas, Ferring, Ipsen, Jansen, Pfizer, Sanofi, Takeda and has received research grants from Astellas and Sanofi; PO has reported institutional honoraria from Janssen, Bayer, Ferring Pharmaceuticals for consultancy and research grants from Merck and Varian; GP has reported

advisory boards/honoraria from AstraZeneca, Bayer, Bristol-Myers Squibb, Ipsen, Janssen, MSD, Novartis and Pfizer; BT has reported paid consultancy for Amgen, Bayer, Astellas, Ferring Pharmaceuticals, Janssen, Sanofi-Genzyme, Steba and that he is an investigator for Bayer, Astellas, Ferring Pharmaceuticals, Myovant Sciences, Janssen, Sanofi-Genzyme and Steba; SG has reported advisory role (including independent data monitoring committees) and speakers bureau for AAA International, Active Biotech AB, Amgen, Astellas Pharma, Bayer, Bristol-Myers Squibb, CellSearch, Clovis, CureVac, Dendreon, ESSA Pharma, Ferring, Innocrin Pharmaceuticals, Janssen Cilag, MaxiVAX, Millenium, Nectar, Novartis, Orion, Pfizer, ProteoMediX, Roche, Sanofi, she has reported being the co-inventor for a method for biomarker discovery (on patent application WO 2009138392 A1, granted in China, Europe, Japan and the US).

REFERENCES

1. Schroder FH, Hugosson J, Roobol MJ et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014; 384: 2027-2035.
2. Vickers AJ, Ulmert D, Sjoberg DD et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study. BMJ 2013; 346: f2023.
3. Thompson IM, Ankerst DP, Chi C et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2006; 98: 529-534.
4. Nam RK, Toi A, Klotz LH et al. Assessing individual risk for prostate cancer. J Clin Oncol 2007; 25: 3582-3588.
5. Kasivisvanathan V, Rannikko AS, Borghi M et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. New England Journal of Medicine 2018; 378: 1767-1777.
6. Rouviere O, Puech P, Renard-Penna R et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019; 20: 100-109.
7. Ahmed HU, El-Shater Bosaily A, Brown LC et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017; 389: 815-822.

8. Kasivisvanathan V, Rannikko AS, Borghi M et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med 2018; 378: 1767-1777.
9. Epstein JI, Egevad L, Amin MB et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40: 244-252.
10. Amin MB, Greene FL, Edge SB et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017; 67: 93-99.
11. D'Amico AV, Whittington R, Malkowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998; 280: 969-974.
12. von Eyben FE, Kairemo K. Meta-analysis of (11)C-choline and (18)F-choline PET/CT for management of patients with prostate cancer. Nucl Med Commun 2014; 35: 221-230.
13. Hofman MS, Lawrentschuk N, Francis RJ et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020; 395: 1208-1216.
14. Corfield J, Perera M, Bolton D, Lawrentschuk N. (68)Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review. World J Urol 2018; 36: 519-527.
15. Bruinsma SM, Bangma CH, Carroll PR et al. Active surveillance for prostate cancer: a narrative review of clinical guidelines. Nat Rev Urol 2016; 13: 151-167.
16. Bill-Axelson A, Holmberg L, Garmo H et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. N Engl J Med 2018; 379: 2319-2329.
17. Wilt TJ, Brawer MK, Jones KM et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012; 367: 203-213.
18. Hamdy FC, Donovan JL, Lane JA et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med 2016; 375: 1415-1424.
19. Widmark A, Klepp O, Solberg A et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009; 373: 301-308.
20. Warde P, Mason M, Ding K et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 2011; 378: 2104-2111.
21. Michalski JM, Moughan J, Purdy J et al. Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. JAMA Oncol 2018; 4: e180039.
22. Dearnaley D, Syndikus I, Sumo G et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol 2012; 13: 43-54.

23. Incrocci L, Wortel RC, Alemayehu WG et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2016; 17: 1061-1069.
24. Roach M, 3rd, Bae K, Speight J et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008; 26: 585-591.
25. Zumsteg ZS, Spratt DE, Pei I et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. Eur Urol 2013; 64: 895-902.
26. Hanks GE, Pajak TF, Porter A et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol 2003; 21: 3972-3978.
27. Bolla M, de Reijke TM, Van Tienhoven G et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009; 360: 2516-2527.
28. Nabid A, Carrier N, Martin AG et al. Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III Trial. Eur Urol 2018; 74: 432-441.
29. Abdollah F, Karnes RJ, Suardi N et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. J Clin Oncol 2014; 32: 3939-3947.
30. Fizazi K, Faivre L, Lesaunier F et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. Lancet Oncol 2015; 16: 787-794.
31. Fizazi KFL, Lesaunier F, Delva R, Gravis G, Rolland F, et al. Updated results of GETUG-12, a phase 3 trial of docetaxel-based chemotherapy in high-risk localized prostate cancer, with a 12-year follow-up. ESMO Abstract 791 2018.
32. Sandler HHC, Rosenthal SA , Sarthor O, Gomella LG, Amn M, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer. J Clin Oncol 2015.
33. James ND, Sydes MR, Clarke NW et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016; 387: 1163-1177.
34. Vale CL, Burdett S, Rydzewska LHM et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol 2016; 17: 243-256.
35. Ahlgren G FP, Tammela TIJ et al. A randomized phase III trial between adjuvant docetaxel and surveillance after radical prostatectomy for high risk prostate cancer. J Clin Oncol 2016.
36. Kellokumpu-Lehtinen ea. ASCO 2018 abstract 5000. 2018.

37. Lin D GM, Aronson W et al. VA CSP#553 Chemotherapy after prostatectomy (cap) for high risk prostate carcinoma: a phase III randomized study. J Urol 2016; 195.
38. Wiegel T, Bottke D, Steiner U et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009; 27: 2924-2930.
39. Van den Broeck T, van den Bergh RCN, Arfi N et al. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. Eur Urol 2019; 75: 967-987.
40. Shipley WU, Seiferheld W, Lukka HR et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. N Engl J Med 2017; 376: 417-428.
41. Carrie C MN, Burban-Provost P, et al. Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for metastatic free survival (MFS) after radical prostatectomy (RP): Update at 9 years of the GETUG-AFU 16 phase III randomized trial (NCT00423475).
. ASCO Meeting Chicago Abstract 5001 2019.
42. Pollack A, Karrison TG, Balogh AG et al. Short Term Androgen Deprivation Therapy Without or With Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiotherapy: The NRG Oncology/RTOG 0534 SPPORT Trial. International Journal of Radiation Oncology Biology Physics 2018; 102: 1605-1605.
43. Perera M, Papa N, Roberts M et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol 2019.
44. Zumsteg ZS, Spratt DE, Romesser PB et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. Eur Urol 2015; 67: 1009-1016.
45. Philippou Y, Parker RA, Volanis D, Gnanapragasam VJ. Comparative Oncologic and Toxicity Outcomes of Salvage Radical Prostatectomy Versus Nonsurgical Therapies for Radiorecurrent Prostate Cancer: A Meta-Regression Analysis. Eur Urol Focus 2016; 2: 158-171.
46. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol 2011; 8: 378-382.
47. Kothari G, Ost P, Cheung P et al. Trends in Management of Oligometastatic Hormone-Sensitive Prostate Cancer. Curr Oncol Rep 2019; 21: 43.
48. Ost P, Reynders D, Decaestecker K et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. J Clin Oncol 2018; 36: 446-453.
49. Palma DA, Olson R, Harrow S et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet 2019; 393: 2051-2058.

50. Duchesne GM, Woo HH, Bassett JK et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol 2016; 17: 727-737.
51. Loblaw DA, Perry J, Chambers A, Laperriere NJ. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the Cancer Care Ontario Practice Guidelines Initiative's Neuro-Oncology Disease Site Group. J Clin Oncol 2005; 23: 2028-2037.
52. Crook JM, O'Callaghan CJ, Duncan G et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012; 367: 895-903.
53. Sweeney CJ, Chen YH, Carducci M et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med 2015; 373: 737-746.
54. Gravis G, Fizazi K, Joly F et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013; 14: 149-158.
55. Kyriakopoulos CE, Chen YH, Carducci MA et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol 2018; 36: 1080-1087.
56. Tucci M, Bertaglia V, Vignani F et al. Addition of Docetaxel to Androgen Deprivation Therapy for Patients with Hormone-sensitive Metastatic Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016; 69: 563-573.
57. Fizazi K, Tran N, Fein L et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2017; 377: 352-360.
58. James ND, de Bono JS, Spears MR et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med 2017; 377: 338-351.
59. Fizazi K, Tran N, Fein L et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol 2019; 20: 686-700.
60. Chi KN, Agarwal N, Bjartell A et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2019; 381: 13-24.
61. Armstrong AJ, Szmulewitz RZ, Petrylak DP et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol 2019; 37: 2974-2986.
62. Davis ID, Martin AJ, Stockler MR et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med 2019; 381: 121-131.
63. Vale CL FD, White IR, et al. What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis. Ann Oncol 2018; 29: 1249-1257.
64. Feyerabend S, Saad F, Li T et al. Survival benefit, disease progression and quality-of-life outcomes of abiraterone acetate plus prednisone versus docetaxel in metastatic hormone-sensitive prostate cancer: A network meta-analysis. Eur J Cancer 2018; 103: 78-87.
65. Boeve LMS, Hulshof M, Vis AN et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy

Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. Eur Urol 2019; 75: 410-418.
66. Parker CC, James ND, Brawley CD et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018; 392: 2353-2366.
67. Coleman R, Body JJ, Aapro M et al. Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol 2014; 25 Suppl 3: iii124-137.
68. Cornford P, Bellmunt J, Bolla M et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol 2017; 71: 630-642.
69. Smith MR, Saad F, Chowdhury S et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med 2018; 378: 1408-1418.
70. Hussain M, Fizazi K, Saad F et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med 2018; 378: 2465-2474.
71. Fizazi K, Shore N, Tammela TL et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med 2019; 380: 1235-1246.
72. Storlie JA, Buckner JC, Wiseman GA et al. Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. Cancer 1995; 76: 96-100.
73. Venkitaraman R LD, Murthy V et al. A randomised phase 2 trial of dexamethasone versus prednisolone in castration-resistant prostate cancer. Eur Urol 2015; 67: 673-679.
74. Ryan CJ, Smith MR, Fizazi K et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015; 16: 152-160.
75. Szmulewitz RZ, Peer CJ, Ibraheem A et al. Prospective International Randomized Phase II Study of Low-Dose Abiraterone With Food Versus Standard Dose Abiraterone In Castration-Resistant Prostate Cancer. J Clin Oncol 2018; 36: 1389-1395.
76. Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424-433.
77. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502-1512.
78. Petrylak DP, Tangen CM, Hussain MH et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 351: 1513-1520.
79. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013; 369: 213-223.
80. Cherny NI, Sullivan R, Dafni U et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2015; 26: 1547-1573.
81. Smith M, Parker C, Saad F et al. Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant

prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019; 20: 408-419.
82. EMA restricts use of prostate cancer medicine Xofigo. 2018; 680161.
83. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376: 1147-1154.
84. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995-2005.
85. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187-1197.
86. Khalaf DJ, Annala M, Taavitsainen S et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 2019; 20: 1730-1739.
87. de Wit R, de Bono J, Sternberg CN et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med 2019; 381: 2506-2518.
88. Cuzick J, Swanson GP, Fisher G et al. Prognostic value of an RNA expression signature derived from cell cycle proliferation genes in patients with prostate cancer: a retrospective study. Lancet Oncol 2011; 12: 245-255.
89. Zhao SG, Chang SL, Spratt DE et al. Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. Lancet Oncol 2016; 17: 1612-1620.
90. Antonarakis ES, Lu C, Wang H et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 2014; 371: 1028-1038.
91. Armstrong AJ, Halabi S, Luo J et al. Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration-Resistant Prostate Cancer: The PROPHECY Study. J Clin Oncol 2019; 37: 1120-1129.
92. Robinson D, Van Allen EM, Wu YM et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015; 161: 1215-1228.
93. Castro E, Goh C, Olmos D et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013; 31: 1748-1757.
94. Pritchard CC, Mateo J, Walsh MF et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med 2016; 375: 443-453.
95. Giri VN, Knudsen KE, Kelly WK et al. Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol 2018; 36: 414-424.
96. Mandelker D, Donoghue MTA, Talukdar S et al. Germline-Focused Analysis of Tumour-Only Sequencing: Recommendations from the ESMO Precision Medicine Working Group. Ann Oncol 2019.
97. Mateo J, Carreira S, Sandhu S et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med 2015; 373: 1697-1708.
98. Le DT, Durham JN, Smith KN et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017; 357: 409-413.

99. Abida W, Cheng ML, Armenia J et al. Analysis of the Prevalence of Microsatellite Instability in Prostate Cancer and Response to Immune Checkpoint Blockade. JAMA Oncol 2018.
100. de Bono J, Mateo J, Fizazi K et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2020.
101. Chow E, Harris K, Fan G et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007; 25: 1423-1436.
102. Nguyen QN, Chun SG, Chow E et al. Single-Fraction Stereotactic vs Conventional Multifraction Radiotherapy for Pain Relief in Patients With Predominantly Nonspine Bone Metastases: A Randomized Phase 2 Trial. JAMA Oncol 2019.
103. Saad F, Gleason DM, Murray R et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst 2004; 96: 879-882.
104. Fizazi K, Carducci M, Smith M et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011; 377: 813-822.
105. Bultijnck R, Van de Caveye I, Rammant E et al. Clinical pathway improves implementation of evidence-based strategies for the management of androgen deprivation therapy-induced side effects in men with prostate cancer. BJU Int 2018; 121: 610-618.
106. Liberman UA, Weiss SR, Broll J et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995; 333: 1437-1443.
107. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017; 28: 2340-2366.
108. Dykewicz CA. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. Clin Infect Dis 2001; 33: 139-144. (Adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. Clin Infect Dis 1994;18:421).

Table 1. Stage-matched therapeutic strategies

Localised disease	Low risk	Active surveillance Brachytherapy RP Radical RT
	Intermediate risk	RP Radical RT +/- neoadjuvant ADT Brachytherapy Active surveillance
	High risk	Long term ADT + radical RT +/- neoadjuvant docetaxel RP + pelvic lymphadenectomy
Locally-advanced disease		Neoadjuvant ADT + radical RT + adjuvant ADT +/- neoadjuvant docetaxel RP + pelvic lymphadenectomy
Metastatic disease	Hormone-naive	ADT + abiraterone ADT + docetaxel ADT + enzalutamide ADT + apalutamide RT for low volume ADT alone for frail patients who can not tolerate the above treatments Bone health agent
	Castration-resistant (first line)	Abiraterone Docetaxel Enzalutamide ^{223}Ra for patients unfit for above treatments (and bone-only metastases)
	Second line or post-docetaxel	Abiraterone Cabazitaxel Enzalutamide ^{223}Ra

^{223}Ra, radium-223; ADT, androgen deprivation therapy; RP, radical prostatectomy; RT, radiotherapy

Figure 1. Diagnostic work-up and staging for prostate cancer

CT, computed tomography; DRE, digital rectal examination; GS, Gleason score; mpMRI, multi-parametric magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

[a]In addition to PSA level and MRI results, the decision to biopsy or not should be made in light of DRE findings, ethnicity, age, comorbidities, free/total PSA, history of previous biopsy and patient values.

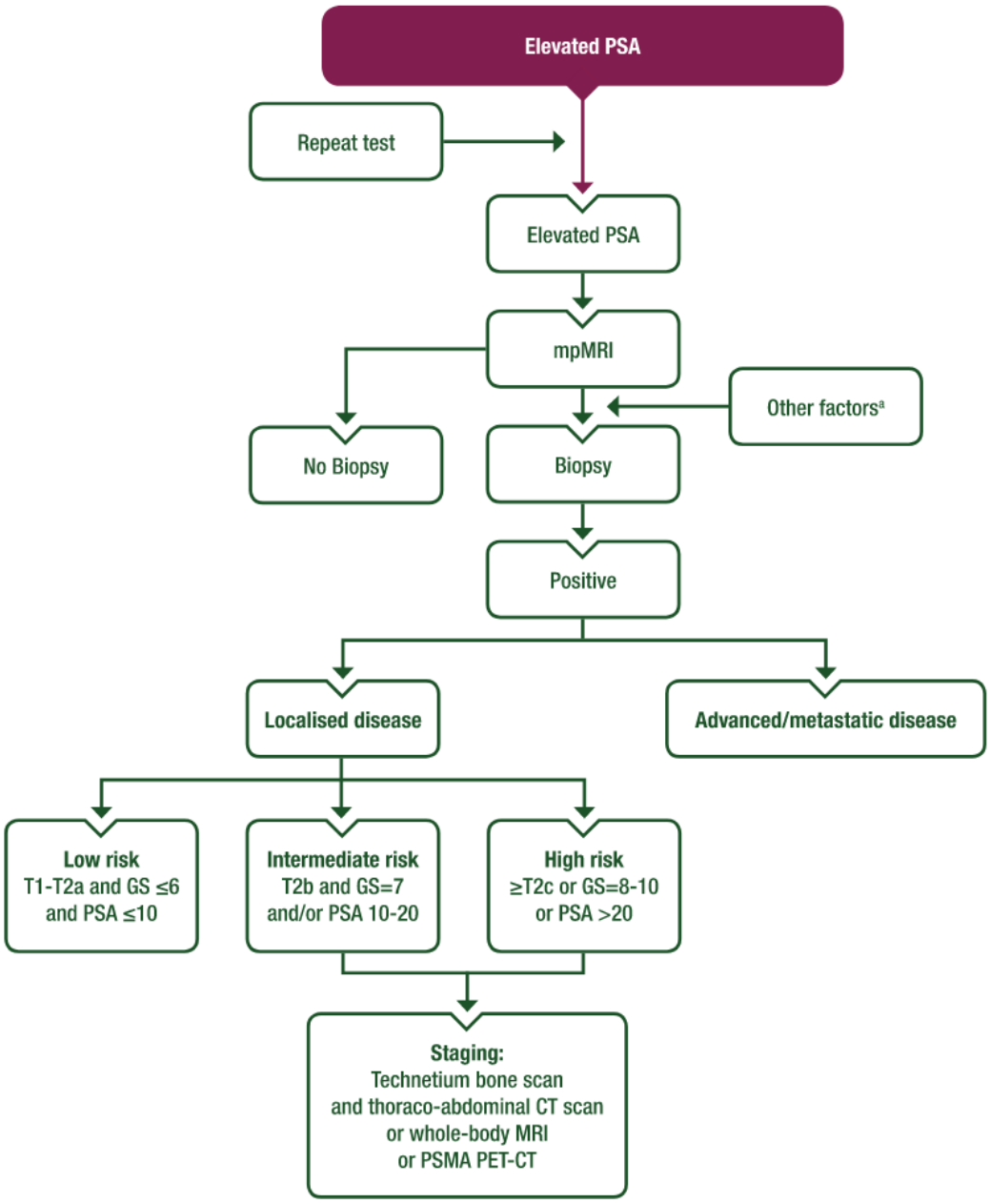

Figure 2. Localised prostate cancer treatment algorithm

ADT, androgen deprivation therapy, EBRT, electron beam radiotherapy; HDR, high-dose rate; HIFU, high-intensity focused ultrasound; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy: RT, radiotherapy.

[a] Also suitable for localised/locally advanced disease if patient not suitable for (or unwilling to have) radical treatment

[b] For men with biochemical relapse and symptomatic local disease, proven metastases or a PSA doubling time of <3 months.

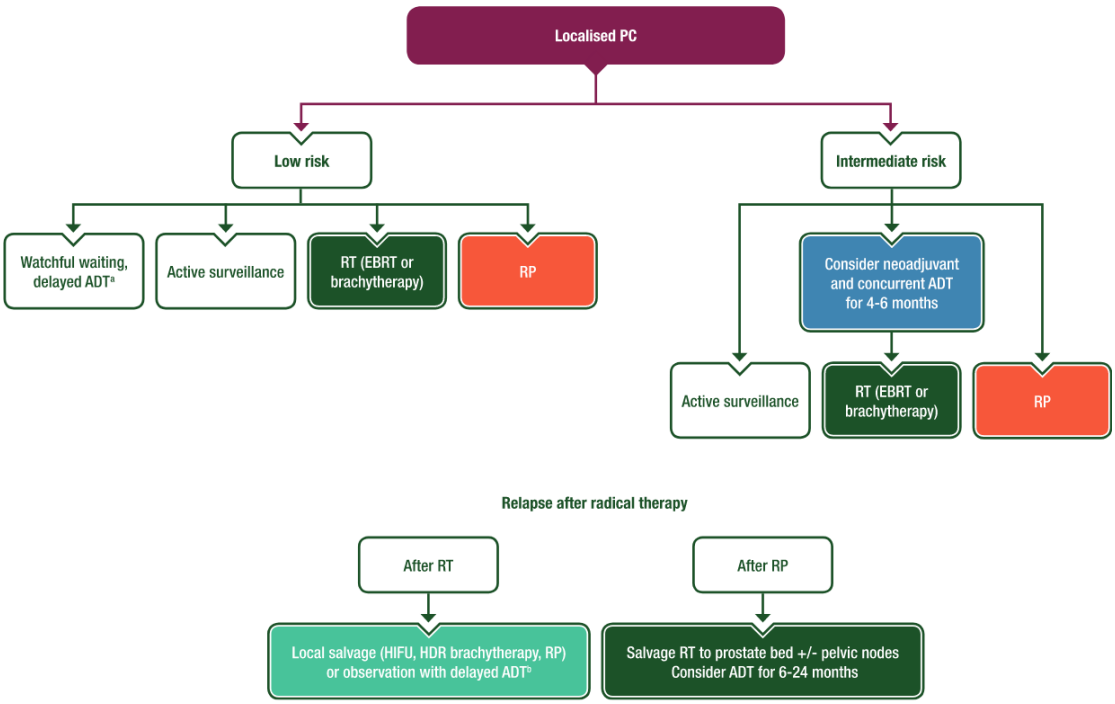

Figure 3. High-risk localised and locally advanced prostate cancer treatment algorithm

ADT, androgen deprivation therapy, EBRT, electron beam radiotherapy; HDR, high-dose rate; HIFU, high-intensity focused ultrasound; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy: RT, radiotherapy.

[a] For men with biochemical relapse and symptomatic local disease, proven metastases or a PSA doubling time of <3 months.

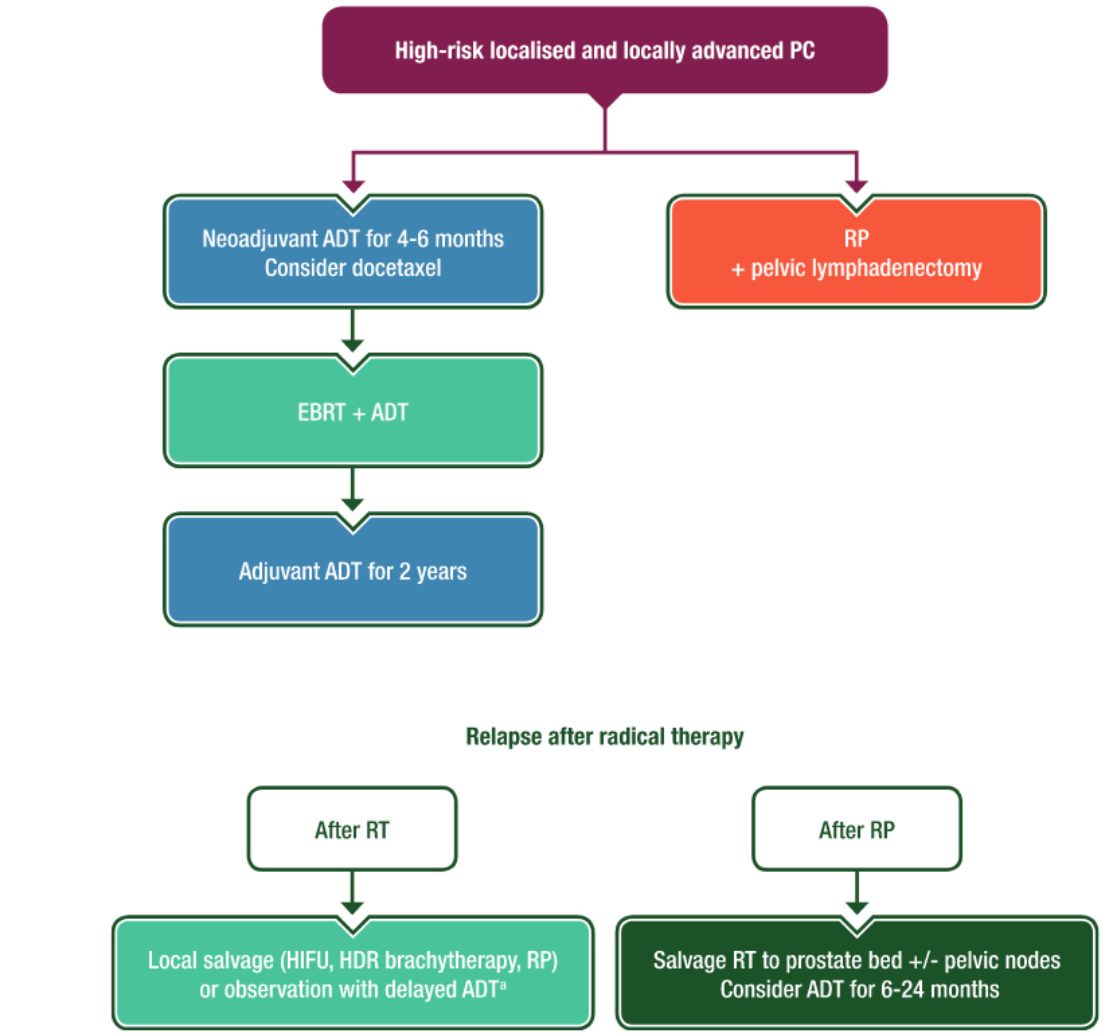

Figure 4. Metastatic prostate cancer treatment algorithm

ADT, androgen deprivation therapy, PC, prostate cancer; RT, radiotherapy.