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Prostate cancer: ESMO Consensus Conference Guidelines 2012

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The first ESMO Consensus Conference on prostate cancer was held in Zurich, Switzerland, on 17–19 November 2011, with the participation of a multidisciplinary panel of leading professionals including experts in methodological aspects. Before the conference, the expert panel prepared clinically relevant questions about prostate cancer in four areas for discussion as follows: diagnosis and staging, management of early localized disease, management of advanced localized disease and systemic disease. All relevant scientific literature, as identified by the experts, was reviewed in advance. During the Consensus Conference, the panel developed recommendations for each specific question. The recommendations detailed here are based on an expert consensus after careful review of published data. All participants have approved this final update.

Key words: consensus, ESMO, prostate cancer

introduction

In Europe in 2008, there were about 328 000 men diagnosed with prostate cancer, the incidence having tripled in the last 40 years [1]. For the same year, there were an estimated 69 000 prostate cancer deaths reflecting the controversy about 'overdiagnosis' and consequently of overtreatment. Early diagnosis after prostate-specific antigen (PSA) testing, the long natural history and the sensitivity of prostate cancers to systemic therapies make it also a disease of high prevalence. Management issues are therefore of importance not only to patients and their doctors, but also to those responsible for planning and managing healthcare systems. There is a large body of clinical literature addressing the management of prostate cancer, and the aim of the Consensus Conference was to produce agreed multidisciplinary evidence-based guidelines on selected relevant clinical questions.

methods

In 2010, European Society for Medical Oncology (ESMO) decided to update the ESMO clinical recommendations in prostate cancer through a consensus process [2]. A Consensus Conference chairperson (A. Horwich) and four working group chairs were appointed; each subgroup comprised six to eight participants with multidisciplinary experiences. A total of 26 experts were involved in this consensus process (see Panel members listed in the Appendix).

The four designated subject areas were as follows:

1) Diagnosis and staging (Chair J. Hugosson)
2) Management of early localized disease (Chair T. de Reijke)
3) Management of advanced localized disease (Chair T. Wiegel)
4) Systemic disease (Chair K. Fizazi)

The first ESMO Consensus Conference on Prostate Cancer was held in November 2011 in Zurich. Before the conference, a number of clinically relevant questions were identified for each group, suitable for consensus discussion. Participants reviewed relevant literature in their subject area before the conference. At the conference, in four parallel sessions, each group discussed and reached agreement on recommendations relating to the questions previously chosen. Decisions were based predominantly on studies published in peer-reviewed journals. If no relevant published data were identified, expert opinions were considered. The consideration of abstracts was at the discretion of the groups, but greater reliance was placed on peer-reviewed publications. All relevant scientific literature, as identified by the experts, was considered. A systematic literature search was not carried out. The recommendations from each group were then presented to all the experts and discussed, and a consensus was reached. The 'Infectious Diseases Society of America-United States Public Health Service Grading System' was used (shown in Tables 1 and 2) for level of evidence and strength of recommendation for each question raised [3].

The consensus in prostate cancer is detailed in this article. The ESMO Clinical Practice Guidelines on Prostate Cancer [4] should be read in conjunction with these additional comments on specific patient situations. Table 3 provides a summary of panel recommendations. The final recommendations listed here have been approved by all participants.

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[†]See Appendix for members of the Panel.

Table 1. Level of evidence [3]

I	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Table 2. Strength of recommendation [3]

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

1. should PSA screening be recommended for all asymptomatic men?

Whether asymptomatic middle-aged men should be screened for prostate cancer by means of the blood test PSA has been subject for debate during the last two decades. Prostate cancer screening guidelines vary widely among countries and medical organizations [5]. The U.S. Preventive Services Task Force (USPSTF) recently made a recommendation against prostate cancer screening, concluding that 'there is moderate or high certainty that screening has no net benefit or that the harms outweigh the benefits' [6, 7]. Although to date, there is insufficient evidence to recommend widespread population-based PSA screening, an editorial in the *New England Journal of Medicine* that followed the USPSTF report suggested a grade C instead of a D 'Strength of recommendation' (Table 2) based on the same evidence, indicating that 'there may be considerations that support providing the service in an individual patient' [8]. Although national routine screening is generally not advocated, most guidelines such as the European Association of Urology, the American Urological Association and the American Cancer Society focus on the individual's perspective and on shared decision making, in a discussion where the patient is informed about pros and cons [9–11].

To date, six randomized trials are published [12–19], three of which were originally designed to evaluate prostate cancer mortality [15, 18, 19]. A meta-analysis has also been published [20]. The magnitude of the risk reduction on disease-specific mortality is comparable or even greater than the effect of mammography in breast cancer screening or fecal occult blood test or sigmoidoscopy in colorectal cancer screening, with a comparable number needed to be invited to screening to prevent one death from the disease [19]. However, PSA screening is associated with overdiagnosis and the quality-of-life aspects are several. The ethical considerations can be difficult, cost-effectiveness and cost-benefit analyses are not demonstrated, and the balance between harms and benefit is not clearly established. On an individual basis, opportunistic PSA testing should follow shared decision making between the individual and the physician's judgment, balancing the harms and benefits with individual considerations. Elderly men and men with important comorbidities should in general be recommended against PSA screening.

Recommendation 1a: PSA screening should not be encouraged for all asymptomatic men (and population-based screening should not be recommended).
Level of evidence: I.
Strength of recommendation: C.
Recommendation 1b: Well-informed men suitable for screening should have access to PSA-testing upon request. There is inconsistent evidence about screening men <50 years and in the age group 70–75 years. There is evidence that the harms of screening men >75 years outweigh the benefits.
Level of evidence: I.
Strength of recommendation: A/B.

2. should an absolute level of PSA or PSA kinetics be used for selecting men for biopsy?

Today, only biopsy from the prostate can establish the diagnosis of prostate cancer (assuming no metastatic sites are present). PSA has become the most frequent marker used for cancer diagnosis despite several disadvantages. PSA has a rather low specificity and the positive predictive value (PPV) in screening studies (cutoff at 3 ng/ml) has been around 25%, meaning that three of four men with a positive test will be worried unnecessarily and exposed to further workup usually including prostate biopsy. Prostate biopsy is associated with increased anxiety [21] and in 4% febrile infections [22]. It is therefore important to evaluate and develop new or complementary markers with higher specificity without impairing the sensitivity for significant cancers. Another problem with PSA is to establish an optimal cutoff. It is well known that significant cancers are also present in the low PSA range [23]. However, the lower the cutoff, the higher is the risk of detecting nonsignificant cancers and increasing the risk of overdiagnosis [24, 25]. Several complementary tests are available such as different isoforms of PSA and PSA kinetics [26, 27] to improve specificity. However, recent research indicates that at present, no biomarker alone can reduce unnecessary testing and a multivariate approach should be considered [28, 29]. PSA kinetics seems not to improve performance of the PSA test [30].

Recommendation 2a: PSA with a cutoff at 3 ng/ml is the base for selecting candidates for biopsy in men suitable for curative treatment.

Table 3. Summary of recommendations

1. Should PSA screening be recommended for all asymptomatic men?
   Recommendation 1a: PSA screening should not be encouraged for all asymptomatic men (and population-based screening should not be recommended).
   Level of evidence: I
   Strength of recommendation: C
   Recommendation 1b: Well-informed men suitable for screening should have access to PSA testing upon request. There is inconsistent evidence about screening men <50 years and in the age group 70–75 years. There is evidence that the harms of screening men >75 years outweigh the benefits.
   Level of evidence: I
   Strength of recommendation: A/B
2. Should an absolute level of PSA or PSA kinetics be used for selecting men for biopsy?
   Recommendation 2a: PSA with a cutoff at 3 ng/ml is the base for selecting candidates for biopsy in men suitable for curative treatment.
   Level of evidence: I
   Strength of recommendation: A
   Recommendation 2b: PSA kinetics has no role in selecting men for biopsy.
   Level of evidence: II
   Strength of recommendation: D
3. Should clinical factors including age, symptoms, family history, comorbidity, DRE and TRUS findings be considered in the decision whether to biopsy?
   Recommendation 3: Clinical factors (age, symptoms, family history, comorbidity, DRE and TRUS findings) should be used in the decision whether to biopsy
   Level of evidence: III
   Strength of recommendation: A
4. Should risk calculators (RCs) and nomograms be used in selecting men for biopsy?
   Recommendation 4: Risk calculators and nomograms can improve efficiency in selecting men for biopsy
   Level of evidence: IV
   Strength of recommendation: C
5. Which patients should have staging of pelvic lymph nodes?
   Recommendation 5a: High-risk patients having a radical prostatectomy should have an extended bilateral lymph node dissection unless prior imaging shows gross multiple lymph node involvement
   Level of evidence: III
   Strength of recommendation: B
   Recommendation 5b: Intermediate risk patients having a prostatectomy should have discussion about risk/benefit of lymph node dissection informed by nomogram estimates.
   Level of evidence: III
   Strength of recommendation: B
   Recommendation 5c: Low-risk patients should not routinely have a pelvic lymph node dissection.
   Level of evidence: III
   Strength of recommendation: D
   Recommendation 5d: Intermediate and high-risk patients to be treated with radiotherapy should have pelvic imaging unless they have had surgical lymph node staging.
   Level of evidence: IV
   Strength of recommendation: B
   Recommendation 5e: Patients evaluated for salvage radiation therapy after prostatectomy should have pelvic imaging, unless low volume and low risk (PSA < 1.0, Gleason score < 7 and slow PSA progression [PSA DT > 15 months]).
   Level of evidence: IV
   Strength of recommendation: B
6. When should a rising PSA trigger treatment?
   Recommendation 6a: Patients on active surveillance should be monitored in the framework of a standardized protocol. A rising PSA or adverse PSA doubling time/PSA velocity should trigger further investigation with a view to active treatment.
   Level of evidence: III
   Strength of recommendation: B
   Recommendation 6b: In a watchful waiting policy, commencement of hormonal therapy should be led by the development of symptoms rather than PSA alone unless the patient is at high risk of complications or rapid progression (e.g. baseline PSA >50 ng/ml and/or PSA doubling time of <12 months).
   Level of evidence: II
   Strength of recommendation: B

Continued

Table 3. *Continued*

Recommendation 6c: Routine PSA determination following radical prostatectomy is necessary to demonstrate biochemical failure early, because there are indications that early salvage radiotherapy can reduce mortality
Level of evidence: III
Strength of recommendation: B
Recommendation 6d: The optimal treatment of biochemical relapse after radical radiotherapy is not known, and radical local salvage treatments may induce considerable toxicity.
Level of evidence: IV
Strength of recommendation: C
Recommendation 6e: Early hormonal therapy is not routinely advised for PSA relapse after local treatments but is an option for those with short PSA doubling time.
Level of evidence: III
Strength of recommendation: C

7. What is the role of IAD (a) in biochemical failure after radiotherapy or (b) for locally advanced disease?
Recommendation 7a: IAD can be offered to patients who are starting salvage androgen deprivation treatment of a rising PSA >1 year following radiotherapy.
Level of evidence: I
Strength of recommendation: C
Recommendation 7b: Patients with locally advanced prostate cancer to be treated with hormonal therapy alone can be offered IAD.
Level of evidence: II
Strength of recommendation: B

8. Which patients gain from radical local treatment?
Recommendation 8a: In low-risk patients, no benefit in overall survival for PSA-detected tumors has been demonstrated. Active surveillance should be discussed and should be an option for these patients.
Level of evidence: II
Strength of recommendation: A
Recommendation 8b: Radical treatment should be discussed with intermediate and high-risk patients, if they have a minimal life expectancy of 10 and 5 years, respectively.
Level of evidence: I
Strength of recommendation: A

9. Are management options for localized prostate cancer equal in efficacy?
Recommendation 9: In patients to be treated with curative intent, options based on either surgery or on radiotherapy should be considered and their possible adverse effects discussed with the patient.
Level of evidence: I/II
Strength of recommendation: B

10. What dose of radiotherapy should be given in localized prostate cancer?
Recommendation 10a: When external beam radiotherapy is used as sole modality, dose escalation to at least 74 Gy increases biochemical control and delays time to salvage hormonal therapy.
Level of evidence: I
Strength of recommendation: A
Recommendation 10b: For salvage radiotherapy following radical prostatectomy treating only biochemical evidence of disease, a dose of at least 66 Gy is recommended.
Level of evidence: IV
Strength of recommendation: B

11. Does combined treatment with hormonal therapy improve the results of radiotherapy in localized prostate cancer?
Recommendation 11a: If moderate dose radiotherapy (<70 Gy) is used for localized intermediate risk prostate cancer, it should be accompanied by 6 months of ADT.
Level of evidence: I
Strength of recommendation: A
Recommendation 11b: In locally advanced prostate cancer (≥T2b) hormone therapy should be used with radiotherapy for at least 6 months and in high-risk patients for at least 24 months.
Level of evidence: I
Strength of recommendation: A
Recommendation 11c: Additional hormone therapy with adjuvant or with salvage radiotherapy following prostatectomy is currently being investigated in prospective trials and is not recommended as standard care
Level of evidence: V
Strength of recommendation: D

Continued

Table 3. *Continued*

12. Is brachytherapy as effective as external beam radiotherapy in early prostate cancer?
    Recommendation 12: Brachytherapy is an effective treatment option for localized prostate cancer
    Level of evidence: III
    Strength of recommendation: B
13. Are sophisticated radiation planning and delivery techniques required for dose-escalated external beam radiotherapy?
    Recommendation 13a: To reduce the adverse effects following radiotherapy, conformal radiotherapy should be used.
    Level of evidence: I
    Strength of recommendation: A
    Recommendation 13b: Intensity-modulated with or without image-guided treatment techniques can be used to reduce normal tissue irradiation
    Level of evidence: III
    Strength of recommendation: B
14. Is radical prostatectomy an option for patients with T3/T4 prostate cancer?
    Recommendation 14: A decision to recommend radical prostatectomy in locally advanced T3-4 prostate cancer should be made only after careful staging and discussion in a multidisciplinary team
    Level of evidence: III
    Strength of recommendation: C
15. Which patients should be offered ART following radical prostatectomy?
    Recommendation 15: Patients with positive surgical margins or extracapsular extension after RP should be informed about the pros and cons of ART
    Level of evidence: I
    Strength of recommendation: A
16. Should radical treatment be applied when positive nodes are found at lymphadenectomy?
    Recommendation 16a: Radical locoregional therapy is recommended for N1 M0 patients suitable for an aggressive management approach
    Level of evidence: III
    Strength of recommendation: B/C
    Recommendation 16b: RT added to ADT is not standard treatment in pN+ patients after radical prostatectomy but may be considered in selected cases.
    Level of evidence: IV
    Strength of recommendation: C
    Recommendation 16c: pN1 patients after radical prostatectomy who are judged to have a high risk for progression should receive immediate ADT.
    Level of evidence: II
    Strength of recommendation: B/C
17. What is the management of non-metastatic castration-resistant prostate cancer?
    Recommendation 17a: Patients with CRPC should continue with life-long androgen deprivation therapy
    Level of evidence: V
    Strength of recommendation: A
    Recommendation 17b: In patients who progress on androgen deprivation, second-line hormone treatments can include the addition of an androgen receptor inhibitor (antiandrogen), antiandrogen withdrawal, estrogen, ketoconazole, or steroids.
    Level of evidence: III
    Strength of recommendation: B
    Recommendation 17c: Patients with CRPC M0, evidence of local progression, and no possibility for local treatment shall be managed like patients with CRPC M1 disease
    Level of evidence: V
    Strength of recommendation: B
18. What standard treatment should be used in metastatic hormone-naive prostate cancer?
    Recommendation 18a: Immediate continuous castration is the preferred treatment option for metastatic hormone-naïve prostate cancer
    Level of evidence: I
    Strength of recommendation: B
    Recommendation 18b: An antiandrogen should be given for 3–4 weeks when starting androgen deprivation with an LHRH agonist for metastatic hormone-naïve prostate cancer, to counteract testosterone flare
    Level of evidence: III
    Strength of recommendation: B
    Recommendation 18c: Intermittent androgen deprivation is not recommended for metastatic hormone-naïve prostate cancer outside of a trial, unless there is significant intolerance of hormone therapy
    Level of evidence: I
    Strength of recommendation: C

Continued

Table 3. *Continued*

Recommendation 18d: Concomitant bone-targeting therapy with either denosumab or a bisphosphonate is not recommended for metastatic hormone-naïve prostate cancer.
Level of evidence: II
Strength of recommendation: C
Recommendation 18e: Concomitant cytotoxic chemotherapy is not recommended for metastatic hormone-naïve prostate cancer outside a clinical trial.
Level of evidence: II
Strength of recommendation: D
19. What are the treatment options in patients with metastatic CRPC?
Recommendation 19a: Docetaxel chemotherapy is appropriate for symptomatic patients with metastatic castration-resistant disease and good performance status and should also be discussed with asymptomatic patients with evidence of rapidly progressing disease
Level of evidence: I
Strength of recommendation: B
Recommendation 19b: Second, third and fourth line hormone manipulations are options to seek short-term responses
Level of evidence: III
Strength of recommendation: B
20. Are there any effective anticancer treatments for those who have failed docetaxel?
Recommendation 20a: Patients with good performance status should have discussion about further anticancer treatment if one of the following is available; cabazitaxel, abiraterone, MDV3100 (enzalutamide), radium-223
Level of evidence: I
Strength of recommendation: A
Recommendation 20b: Patients with good performance status should have discussion about retreatment with docetaxel or second-line chemotherapy with mitoxantrone if they had responded well to previous chemotherapy, unless new effective lower-toxicity agents are available
Level of evidence: III
Strength of recommendation: C
21. Should an antiosteoclastic drug be used in patients with castration-resistant prostate cancer and bone metastases?
Recommendation 21a: In patients with bone metastases from CRPC at high risk for clinically relevant skeletal-related events, denosumab or zoledronic acid can be recommended, and a large trial found that denosumab delayed skeletal-related events for longer than zoledronic acid. Neither agent has been shown to prolong survival
Level of evidence: I
Strength of recommendation: B
Recommendation 21b: In patients with bone metastases from CRPC at high risk for clinically relevant skeletal-related events, neither clodronate nor pamidronate have been shown to have palliative benefit
Level of evidence: I
Strength of recommendation: E
Recommendation 21c: Patients on antiosteoclastic drugs should have monitoring of serum calcium and oral health; patients on zoledronate additionally require monitoring of renal function
Level of evidence: II
Strength of recommendation: A

PSA, prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasound; RCs, risk calculators; IAD, intermittent androgen deprivation; ADT, androgen deprivation therapy; ART, adjuvant radiotherapy; RP, radical prostatectomy; DT, doubling time; CRPC, castration resistant prostate cancer; LHRH, luteinising hormone releasing hormone.

Level of evidence: I.
Strength of recommendation: A.
Recommendation 2b: PSA kinetics has no role in selecting men for biopsy.
Level of evidence: II.
Strength of recommendation: D.

3. should clinical factors including age, symptoms, family history, comorbidity, digital rectal examination and transrectal ultrasound findings be considered in the decision whether to biopsy?

Some screening trials have used digital rectal examination (DRE) as a complement to PSA [13, 14, 17, 31]. It is obvious that DRE will increase specificity, but 75% of detectable cancers in a screening program are nonpalpable [32], and the PPV will be below 50% even in men with PSA >4 ng/ml [33]. Micturition symptoms in men with slightly elevated PSA are usually due to benign prostatic hyperplasia (BPH), and men with elevated PSA and symptoms have a lower risk for prostate cancer compared with men without symptoms [34]. As BPH is the most common condition explaining an elevated PSA, prostate volume is an important risk factor [35] as is the finding of hypoechoic lesions on transrectal ultrasound (TRUS) [36]. Also, family history is related to biopsy outcome [37] but some screening studies have failed to show such a relation [38].

Magnetic resonance imaging (MRI) technology is continuously evolving, and more extensive use of MRI technology in clinical trials and practice will help to improve prostate cancer diagnosis and treatment planning. It is

currently a promising tool but needs further research to establish its role [39–42].

Recommendation 3: Clinical factors (age, symptoms, family history, comorbidity, DRE and TRUS findings) should be used in the decision whether to biopsy.
Level of evidence: III.
Strength of recommendation: A.

4. should risk calculators and nomograms be used in selecting men for biopsy?

Statistical models such as the Prostate Cancer Prevention Trial risk calculator (PCPT-RC) [43] and the European Randomized Study of Screening for Prostate Cancer risk calculators [44, 45] have been developed to combine risk factors in the estimate of cancer risk in an individual, in order to help in targeting subgroups where biopsy is more likely to detect cancer [46]. Several nomograms have been constructed and 10 European and US cohorts belonging to the Prostate Biopsy Collaborative Group have tried to validate them. Validation of the PCPT-RC failed in all cohorts except for one of the US cohorts. In all five ERSPC cohorts, there was little benefit to using PCPT calculated risks of positive biopsy. There was some benefit at limited PCPT-RC risk ranges in other cohorts. The areas under the receiver operating characteristic curves of the ERSPC DRE-based RC ranged from 0.61 to 0.77 and were substantially higher in each of the six cohorts than those of a model based on only PSA and DRE (ranging from 0.56 to 0.72) [35, 47].

Recommendation 4: Risk calculators and nomograms can improve efficiency in selecting men for biopsy.
Level of evidence: IV.
Strength of recommendation: C.

5. which patients should have staging of pelvic lymph nodes?

There are a number of uncertainties associated with pelvic lymph node staging, including the sensitivity of imaging as an alternative, the therapeutic benefit of lymphadenectomy and how extensive the procedure should be.

Evaluation of *N*-stage is only indicated in men who are under consideration for curative treatment. Presence of gross and/or multiple nodal metastasis is usually a contraindication to curative treatment, while patients with limited lymph node spread are considered candidates for either radical prostatectomy (RP) with extended lymph node dissection or radiation with pelvic fields [48, 49]. The presence of nodal metastasis is most accurately evaluated by lymph node dissection. The limited node dissection of just the obturator fossa is regarded as unsatisfactory as it misses half of all metastases present [50].

How extended a lymph node dissection should be is not established, but an extended dissection is associated with a higher complication rate, especially lymphoceles and lymphoedema [51, 52]. Replacing surgical staging with imaging would therefore be valuable. Even though imaging by CT scan or MRI has improved, these techniques still identify at best 50% of patients with lymph node metastasis [53]. New techniques and risk nomograms [54] are developing but it is doubtful that they are sensitive enough to replace surgical staging [55]. However, the majority of men who are treated by prostatectomy for localized prostate cancer are those with a low risk of lymph node spread.

Use of nomograms can be helpful to establish the individual risk, but populations seem to differ probably due to a stage shift over time not entirely reflected by the risk factors, PSA, T-stage and Gleason score [56]. Patients with PSA <20, T-stage <T2b and Gleason score < 7 have a low risk (<10%) for lymph node metastasis and could be spared a surgical staging [57, 58]. Also patients with a limited Gleason 4 pattern could be regarded as a low-risk group [59].

The choice between an extended lymph node dissection with high sensitivity and a potential for better outcome but with a high risk of complications should be weighed against an imaging procedure with much lower sensitivity but negligible side-effects and lower costs. The optimal staging procedure in different situations remains to be defined. Both CT and MRI have a low and similar sensitivity for detecting lymph node metastasis of around 40%. However, grossly involved lymph nodes (diameter > 2 cm) are diagnosed with high sensitivity.

Patients with relapsing disease after RP should be considered for pelvic staging before salvage radiation therapy (SRT). In this situation, only imaging is feasible. As PSA is much more sensitive for tumor relapse than any imaging technique and radiation therapy (RT) usually is considered as early as possible, pelvic staging is questionable in patients with a low risk of metastatic disease (Gleason score < 7 and long PSA doubling time >15 months) [60].

Recommendation 5a: High-risk patients having a RP should have an extended bilateral lymph node dissection unless prior imaging shows gross multiple lymph node involvement.
Level of evidence: III
Strength of recommendation: B
Recommendation 5b: Intermediate risk patients having a prostatectomy should have discussion about risk/benefit of lymph node dissection informed by nomogram estimates.
Level of evidence: III
Strength of recommendation: B
Recommendation 5c: Low-risk patients should not routinely have a pelvic lymph node dissection.
Level of evidence: III
Strength of recommendation: D
Recommendation 5d: Intermediate and high-risk patients to be treated with radiotherapy should have pelvic imaging unless they have had surgical lymph node staging.
Level of evidence: IV
Strength of recommendation: B
Recommendation 5e: Patients evaluated for SRT after prostatectomy should have pelvic imaging, unless low volume and low risk (PSA < 1.0, Gleason score < 7 and slow PSA progression (PSA doubling time > 15 months)).

Level of evidence: IV
Strength of recommendation: B

6. when should a rising PSA trigger treatment?

PSA is currently the best tumor marker available to monitor tumor progression and tumor recurrence following curative treatment. Also, in order to reduce overtreatment some patients with localized disease are not immediately treated, but rather are followed in an active surveillance program where PSA combined with imaging and re-biopsies are used as markers and triggers to start treatment with curative intent. It is now recognized that overtreatment is a serious problem in patients diagnosed with prostate cancer, especially when diagnosed following PSA measurement in an asymptomatic patient. Active surveillance can be offered to patients with a low tumor burden (one or two biopsy cores positive, Gleason score < 7, PSA < 10 ng/ml) [61]. There is no single standardized protocol for active surveillance, and different PSA values and PSA kinetics are being used as an indication for active treatment [62]. Phase III protocols comparing active surveillance and immediate treatment are in progress, but data will not be available for some years.

Patients with locally advanced disease who are not candidates for treatment with curative intent can be followed in a watchful waiting program, meaning that treatment is started only when symptoms develop. PSA is thus not a decisive factor. A phase III trial comparing immediate and delayed hormonal treatment demonstrated that there was no difference in prostate cancer mortality or symptom-free survival, but a modest significant difference was found in favor of immediate treatment concerning an increase in overall survival (OS) [63]. In a further analysis of this study, it was found that patients with a baseline PSA of >50 ng/ml and/or a PSA doubling time of <12 months were at an increased risk of death from prostate cancer and might be candidates for immediate hormonal treatment [64].

After curative treatment of clinically localized prostate cancer, biochemical recurrence is usually the first evidence of either local recurrence or metastatic progression. PSA recurrence in men undergoing treatment with curative intent is observed in ~30%–40% of the patients [65]. Following RP, biochemical recurrence is defined as a confirmed PSA level >0.2 ng/ml [66] and following radiotherapy the generally accepted definition of biochemical recurrence is of the nadir PSA plus 2 ng/ml [67]. Following RP a sequential rise in lower levels of PSA as detected by ultrasensitive assays can be significant, and patients should be referred for salvage radiotherapy as soon as a biochemical failure is established [68, 69]. The dilemma is to determine whether the biochemical recurrence after surgery or radiation is due to a local or distant relapse. Some factors such as lower Gleason score, long time from treatment to PSA relapse, and long PSA doubling time are indicative for local failure [70, 71]. Important clinical factors discriminating local from distant failure are timing of the PSA increase after surgery (>3 years), PSA doubling time (>11 months), pathological stage (≤pT3a N0) and Gleason score of the prostatectomy specimen (≤6). Imaging to detect metastatic lesions at very low PSA levels (<1.0 ng/ml) is not usually helpful.

SRT should be considered for men presenting with persistent PSA after prostatectomy or with PSA relapse. Several studies have demonstrated the importance of a low pre-salvage radiation PSA level to obtain the best results [69, 72–74]. An ASTRO consensus paper from 1999 concluded that a dose of 64 Gy should be given to the prostatic bed before the PSA had risen to 1.5 ng/ml [72]. More recently, Stephenson et al. [69] reported the results of 1540 patients from 16 contributors. These patients received SRT with a median dose of 66 Gy and had a median follow-up of 53 months. A 6-year biochemical progression-free survival rate of 48% could be achieved when the PSA was <0.5 ng/ml compared with only 18%, when the preradiation therapy PSA was >1.5 ng/ml. In the whole series, the 6-year progression-free survival rate was 32%. The authors identified several prognostic factors that were associated with a poor response to radiation therapy including Gleason score of 8–10, preradiation PSA >2 ng/ml, negative surgical margins, postoperative PSA doubling time of <10 months and seminal vesicle invasion. Patients without these adverse features had a 6-year progression-free survival rate of 69%. A recent single-institution, retrospective analysis provided evidence that salvage radiotherapy may reduce prostate-cancer-specific mortality and that the benefit was most with a PSA doubling time of <6 months, in contrast to the data mentioned above [75]. It is important to point out that achieving an undetectable PSA after SRT is an independent predictor of the outcome and offers a second chance of cure [76].

Local failure after radiotherapy should be confirmed by prostatic biopsy, but only in men in whom a salvage procedure is contemplated. Most recent salvage RP series comprise only moderate numbers from single institutions [77]; however, a retrospective multi-institutional cohort analysis of salvage radical prostatectomies in 404 men with a median of 4.4-year follow-up reported that about 37% were likely to remain recurrence-free [78]. In general, salvage RP can be considered in cases where there was originally organ-confined prostate cancer ≤ T2, Gleason score < 7 and a PSA < 10 ng/ml. Such surgery should be carried out in high-volume centers only. Several new salvage approaches are now being reported (e.g. HIFU, cryotherapy, focal therapy), but all of these should be considered experimental and patients should preferably be treated within a defined protocol.

Androgen deprivation therapy (ADT) in case of a relapse following RP or radiotherapy has been evaluated in retrospective series. It appears that patients may have a long survival even if hormonal treatment is delayed until evidence of metastases, although in a matched cohort analysis a slight improvement in cancer-specific survival was found with early intervention [65, 79, 80]. However, even in higher-risk patients (Gleason score ≥ 7 and PSA doubling time of ≤12 months), Moul et al. [81] observed no survival benefit, although time to clinical metastases was delayed by early androgen treatment.

Recommendation 6a: Patients on active surveillance should be monitored in the framework of a standardized protocol. A

rising PSA or adverse PSA doubling time/PSA velocity should trigger further investigation with a view to active treatment.
Level of evidence: III
Strength of recommendation: B
Recommendation 6b: In a watchful waiting policy, commencement of hormonal therapy should be led by the development of symptoms rather than PSA alone unless the patient is at high risk of complications or rapid progression (e.g. baseline PSA > 50 ng/ml and/or PSA doubling time of <12 months).
Level of evidence: II
Strength of recommendation: B
Recommendation 6c: Routine PSA determination following RP is necessary to demonstrate biochemical failure early, because there are indications that early salvage radiotherapy can reduce mortality.
Level of evidence: III
Strength of recommendation: B
Recommendation 6d: The optimal treatment of biochemical relapse after radical radiotherapy is not known, and radical local salvage treatments may induce considerable toxicity.
Level of evidence: IV
Strength of recommendation: C
Recommendation 6e: Early hormonal therapy is not routinely advised for PSA relapse after local treatments but is an option for those with short PSA doubling time.
Level of evidence: III
Strength of recommendation: C

7. what is the role of intermittent androgen deprivation (a) in biochemical failure after radiotherapy or (b) for locally advanced disease?

Hormonal therapy for metastatic disease should be considered palliative treatment, and it is well known that lowering of testosterone will improve the quality of life of the patient by relieving symptoms, but may be associated with short- and long-term adverse effects [82–88].

As continuous androgen deprivation induces the development of androgen-independent prostate cancer cells, the concept of intermittent androgen deprivation (IAD) has been explored [89]. Based on the preclinical data, it was hoped that IAD would improve OS and would also prevent the deleterious effects of long-term androgen deprivation treatment and consequently reduce costs. Most of the phase II/III studies have been carried out in locally advanced or metastatic disease. Until now, none of the trials has been able to show a survival benefit for IAD [90]. Comparison of different trials, however, is difficult since no standard scheme for IAD has been defined concerning when to start IAD, the duration of each cycle of treatment and time to restart treatment. IAD is only beneficial for those patients who have a sufficient time off therapy. IAD will have implications for the follow-up schedule and the investigations that have to be carried out.

What is the role of IAD treatment in biochemical failure following treatment with curative intent? IAD was studied in a randomized trial which included 1386 patients with a PSA at relapse of >3.0 ng/ml more than 1 year after radical or salvage radiotherapy plus or minus neo/adjuvant hormonal therapy (≤1-year duration) for localized prostate cancer. The primary end point in this trial was OS. The hot flashes in the IAD arm were less and several quality-of-life domains were also improved. The median OS was 8.8 and 9.1 years for the IAD and continuous androgen deprivation arm, respectively. Hence, IAD was noninferior to continuous androgen deprivation [91]. Two other studies are not yet published, so no strong recommendation can be made. One study was in patients following RP [92] and the second study was in patients with a biochemical recurrence following RP, external beam radiation, brachytherapy or high-intensity focused ultrasound [93].

What is the role of IAD treatment in locally advanced/metastatic disease? Several phase II and III trials have studied the role of IAD in this situation. In the South European Oncology Group study [94], patients with locally advanced or metastatic disease were randomized after a 3-month induction treatment and eventually 626 of 766 patients were randomized between IAD and continuous androgen deprivation treatment. Men in the IAD arm reported better sexual activity and had a mean time off hormone therapy of 52 weeks. There was no difference in survival (more prostate cancer deaths, but less cardiovascular deaths in the IAD arm). A Finnish trial [95] led to 554 patients randomized after 24 weeks of androgen deprivation, and did not find any difference in cancer deaths. A smaller European trial randomized 173 patients and again found no difference in progression-free or in OS; also there was little difference in quality-of-life measures [96].

Recommendation 7a: IAD can be offered to patients who are starting salvage androgen deprivation treatment of a rising PSA >1 year following radiotherapy.
Level of evidence: I
Strength of recommendation: C
Recommendation 7b: Patients with locally advanced prostate cancer to be treated with hormonal therapy alone can be offered IAD.
Level of evidence: II
Strength of recommendation: B

8. which patients gain from radical local treatment?

Several curative treatment options are available for patients presenting with localized prostate cancer utilizing different treatment methods (open, laparoscopic and robot-assisted laparoscopy prostatectomy; external beam radiation, brachytherapy). Active surveillance is now an alternative to initial radical treatment in cases with low risk of progression (e.g. ≤2 biopsies positive, PSA < 10 ng/ml, Gleason score 6), and this has become particularly appropriate since screening studies have shown that overtreatment is a serious problem

since up to 40% of the patients would not have needed treatment [97].

All patients with more advanced localized disease (T3/4 N0M0) with a life expectancy of at least 5 years should receive treatment with curative intent. Most patients are treated with a combination of radiation therapy and ADT. The OS of this combination therapy is superior when compared with radiation therapy alone [98–100] and also when compared with ADT alone [101, 102].

Recommendation 8a: In low-risk patients, no benefit in OS for PSA-detected tumors has been demonstrated. Active surveillance should be discussed and should be an option for these patients.
Level of evidence: II
Strength of recommendation: A
Recommendation 8b: Radical treatment should be discussed with intermediate and high-risk patients, if they have a minimal life expectancy of 10 and 5 years, respectively.
Level of evidence: I
Strength of recommendation: A

9. are management options for localized prostate cancer equal in efficacy?

Localized prostate cancer includes stages T1–3 N0 M0. No well-designed randomized prospective trials have been reported comparing surgery and radiation therapy or the different treatment methods, although comparative series have not shown consistent differences between the approaches [103–105].

The Scandinavian Prostate Cancer Collaborative Group trial compared RP and watchful waiting in patients with clinically detected prostate cancers, demonstrating an improved OS in those patients treated with radical surgery [106]. Recently, the outcome of another trial comparing RP to watchful waiting ($n = 731$) has been reported for men with clinically localized prostate cancer, showing no benefit in OS for active treatment in PSA-detected tumors, except for a subgroup of high-risk patients [107]. The PROTECT trial has completed recruitment of men with PSA-detected cancers comparing active monitoring, RP and radiation treatment, but no data are available yet [108].

Comparison of the patterns of side-effects and their development over time following the different treatment modalities should be discussed with the patients when counseling about management decisions [109, 110].

New minimal invasive procedures (high-intensity-focused ultrasound, cryotherapy, focal treatment etc.) have been reported, but the follow-up is too short and comparative studies to standard treatment are lacking. These procedures should be regarded as investigational treatment options that preferably should be carried out within the framework of a trial.

Recommendation 9: In patients to be treated with curative intent, options based on either surgery or on radiotherapy should be considered and their possible adverse effects discussed with the patient.
Level of evidence: I/II
Strength of recommendation: B

10. what dose of radiotherapy should be given in localized prostate cancer?

Owing to improvements in radiotherapy (conformal, intensity-modulated and image-guided techniques), it is now possible to increase the dose while keeping side-effects at acceptable levels. Doses between 74 and 78 Gy have been compared with 64–70 Gy in several randomized, controlled trials showing significant improvements in biochemical control rates and delay in use of salvage hormone treatment (HT) comparing radiotherapy alone or in combination with androgen suppression. There is no obvious heterogeneity of advantage between patient risk groups. However, benefits in overall and metastases-free survival have not yet been proven [111–115]. Especially when used alone, the radiation dose with conventional fractionation should be at least 70 Gy and can be as high as 79 Gy [114, 116–118] and may prolong distant-metastasis-free survival [119, 120]. To limit the increase in side-effects, the use of modern radiation techniques such as intensity-modulated radiotherapy and image-guided radiotherapy is encouraged at higher doses [121]. Hypofractionated schedules are being investigated with appropriate dose adjustments [122].

There is a controversy about the best radiation dose for salvage radiotherapy after prostatectomy (SRT). An established standard is conformal radiotherapy to the prostatic fossa with a dose of about 66 Gy. However, some recently published series demonstrated a better outcome with higher total doses [123–127], and this is supported by radiobiological data [125]. Data from randomized phase III trials are not yet available. Bernard et al. [127] investigated 364 men with SRT after RP after a median follow-up of 6.0 years. They identified three dose groups (low: <64.8 Gy, moderate: 64.8–66.6 Gy, high: >66.6 Gy). In multivariate analysis they found that compared with the high dose level, there was decreased biochemical control for patients treated with the low dose level [hazard ratio (HR) 0.60].

Siegmann et al. [126] also reported a series including 301 patients; 234 received 66.6 Gy while 67 patients with a PSA decrease during SRT were selected and irradiated up to 70.2 Gy. In the multivariate analysis, the total dose was a significant predictor of reduced risk of biochemical progression ($P = 0.017$).

Recommendation 10a: When external beam radiotherapy is used as sole modality, dose escalation to at least 74 Gy increases biochemical control and delays time to salvage hormonal therapy.
Level of evidence: I
Strength of recommendation: A
Recommendation 10b: For salvage radiotherapy following RP treating only biochemical evidence of disease, a dose of at least 66 Gy is recommended.
Level of evidence: IV
Strength of recommendation: B

11. does combined treatment with hormonal therapy improve the results of radiotherapy in localized prostate cancer?

In order to improve outcome, especially in intermediate and high-risk patient groups, combinations of neo- or adjuvant hormonal therapy have been explored. It has been shown that in patients with localized prostate cancer, but with unfavorable risk factors, the addition of 6 months of androgen deprivation improves disease control, metastases-free survival, cancer-specific survival and OS. These studies have used prostate doses <70 Gy, and presently, there is inadequate data to know if patients receiving higher doses benefit from combined modality treatment.

For high-risk cancers, there is abundant level I evidence that the combination of RT and ADT leads to significantly higher OS rates when compared with RT alone [98–100] and to ADT alone [101, 102]. There is no exact definition of the optimal duration of ADT, but there is evidence that long-term ADT is superior when compared with short-term ADT (24–36 versus 4–6 months) [128–130]. Therefore, high-risk patients should receive at least 24 months of ADT after radiotherapy. There is no evidence that prolonging ADT beyond 24–36 months adds further benefit. Though also active in this setting, there is no direct evidence that the administration of antiandrogen monotherapy as adjuvant to radiotherapy equals the OS benefit obtained with long-term luteinising hormone releasing hormone (LHRH) analogs. However, in patients with pre-existing cardiovascular morbidity, the administration of long-term LHRH analogs should be adopted with caution as an increased risk of cardiovascular mortality in these patients has been suggested. In these patients, the use of bicalutamide 150 mg can be defended based on the results from the EPC trial [131].

Should HT be given to patients treated with adjuvant RT to the prostate bed? With the subclinical cancer burden treated in this clinical situation, there is no prospective data supporting the need for adjuvant androgen suppression in combination with adjuvant radiotherapy (ART). In the ongoing European Organization for Research and Treatment of Cancer (EORTC) trial (22043), patients with pathological stage pT2R1 or pT3a-b and undetectable PSA will be randomized after prostatectomy between postoperative radiation alone or postoperative radiation and short-term adjuvant androgen deprivation for 6 months. The question is also being addressed in the RADICALS trial [132].

In case of salvage radiotherapy (SRT) for PSA failure after prostatectomy, interesting retrospective data raise the question of androgen deprivation during and after SRT. Choo et al. [133] reported on 75 patients treated with SRT and 2-year androgen deprivation treated in a pilot prospective study. With a median follow-up of 6.5 years, relapse-free survival rate at 7 years was 78% of the whole population. A group at the University of Michigan reported on 630 men after SRT. Sixty-six percent had high risk factors, and the mean radiation therapy dose was 68 Gy. Twenty-four percent of all patients received concurrent androgen deprivation (median duration of 11 months). With a median follow-up of 3 years, androgen deprivation was shown to be a significant independent predictor of progression-free survival in the high-risk group ($P < 0.05$) [134]. Similarly, benefit of 6 months androgen deprivation in terms of bRFS (biochemical relapse-free survival) was shown in a retrospective analysis of 138 patients treated at a single European center [135]. However, the optimal duration of this ADT remains uncertain.

The only randomized trial is RTOG 96–01, a multicenter phase III trial designed to compare antiandrogen therapy (bicalutamide monotherapy 150 mg/day) and SRT ($n = 387$) to a placebo and SRT ($n = 383$) in men with pT3 ($n = 518$)/pT2 R1 ($n = 252$) N0 M0 prostate cancer and reported so far in abstract. The median follow-up in surviving patients was 7.1 years. The addition of 24 months of bicalutamide during and after RT significantly improved freedom from PSA progression from 40% to 57% ($P < 0.0001$) and reduced the incidence of metastasis (7.4% versus 12.6%, $P < 0.04$) without adding significantly to radiation toxicity, but definitive results are pending [136]. Therefore, there are currently no clear conclusions from these data. Possibly high-risk patients profit from additional antiandrogen therapy.

Recommendation 11a: If moderate dose radiotherapy (<70 Gy) is used for localized intermediate risk prostate cancer, it should be accompanied by 6 months of ADT.
Level of evidence: I
Strength of recommendation: A
Recommendation 11b: In locally advanced prostate cancer (≥T2b), hormone therapy should be used with radiotherapy for at least 6 months, and in high-risk patients for at least 24 months.
Level of evidence: I
Strength of recommendation: A
Recommendation 11c: Additional hormone therapy with adjuvant or with salvage radiotherapy following prostatectomy is currently being investigated in prospective trials and is not recommended as standard care.
Level of evidence: V
Strength of recommendation: D

12. is brachytherapy as effective as external beam radiotherapy in early prostate cancer?

Brachytherapy is an established treatment of patients with localized prostate cancer. Low dose rate permanent implants are especially indicated in low-risk disease and high dose rate nonpermanent implants, sometimes with external beam RT, in intermediate and high-risk patients [137, 138]. Unfortunately, there are no randomized trials comparing these treatment modalities with surgery or modern external beam radiation. A single institution trial in a range of localized prostate cancers [139] compared external beam radiotherapy alone (55 Gy in 20 fractions) with a combined high dose rate brachytherapy boost and external beam radiotherapy. Though the brachytherapy arm resulted in an improved bRFS compared with external beam radiotherapy alone, and also less acute rectal toxicity, the external beam techniques were suboptimal in that half the patients did not have conformal radiotherapy. A retrospective single institution comparison of high dose IMRT with IMRT

and a brachytherapy boost suggested improved PSA control in those receiving brachytherapy [140]. Another retrospective study of 853 patients treated at the Mayo Clinic in Arizona suggested that any dose escalation improved disease control in intermediate risk prostate cancer, but that IMRT appeared to have less GU toxicity than brachytherapy [141].

Recommendation 12: Brachytherapy is an effective treatment option for localized prostate cancer.
Level of evidence: III
Strength of recommendation: B

13. are sophisticated radiation planning and delivery techniques required for dose-escalated external beam radiotherapy?

Bowel side-effects increase with dose escalation although they may be moderated by improved radiotherapy technique. A phase III trial compared conventional and conformal prostate radiotherapy showing a reduction of Grade 2 side-effects from 15% to 5%; the prostate dose was 64 Gy [121, 122, 142, 143].

Intensity modulated (IMRT) and image guided (IGRT) techniques, usually using fiducial markers, may give improved dose distributions and allow for reduced 'safety margins' and so smaller target volumes. These methods have not been tested against simpler techniques in phase III trials, but comparative clinical side-effect data appear favorable and the methods have been widely introduced.

Recommendation 13a: To reduce the adverse effects following radiotherapy, conformal radiotherapy should be used.
Level of evidence: I
Strength of recommendation: A
Recommendation 13b: Intensity-modulated with or without image-guided treatment techniques can be used to reduce normal tissue irradiation.
Level of evidence: III
Strength of recommendation: B

14. is radical prostatectomy an option for patients with t3/t4 prostate cancer?

Most patients with locally advanced T3–4 prostate cancer are treated with a combination of radiotherapy and ADT; however, there is evidence that RP results in a high 10-year cause-specific survival (CSS), mostly in T3 tumors and in selected patients [144–148]. RP should be reserved for younger patients and/or patients in good physical condition. About 20% have been found to have pT2 tumors at pathological examination. Modern imaging with magnetic resonance improves accuracy of local T3 staging [149]. Any decision to perform surgery should be discussed in a multidisciplinary team involving urologic surgeons, radiologists and oncologists. Patients should be informed that there is a high chance that postoperative treatment (ART, ADT or a combination of both) will be necessary, with the risk of side-effects additional to those of surgery. A (modified) extended lymph node dissection is recommended in these patients [48, 150], although any benefit may derive from more accurate staging rather than the resection itself.

In a matched pair analysis, 191 patients with pT3B disease who received immediate adjuvant ADT were matched with a control group receiving no adjuvant ADT. The 10-year bRFS, metastatic-free survival and CSS were significantly improved in the immediate ADT group, but there was no OS benefit (75% for the immediate group versus 69% for the control group) [151]. Spahn et al. [152] retrospectively analyzed the data of 372 high-risk patients treated with RP. Of them, ADT was initiated if pT3B disease and/or pN+ disease were present. At 10 years, progression free survival (PFS), CSS and OS were 79%, 87% and 72%, respectively. The authors concluded that the combination of RP with stage-dependent ADT led to excellent long-term oncologic results.

In a systematic review of the literature, Shelley et al. [153] concluded that there was no OS benefit for immediate adjuvant ADT (both LHRH and antiandrogens) after prostatectomy. In contrast, there was a highly significant advantage concerning 10-year disease-free survival for the immediate ADT, with an odds ratio of 3.73 (95% CI 2.30–6.03; $P < 0.00001$) [153].

Recommendation 14: A decision to recommend RP in locally advanced T3-4 prostate cancer should be made only after careful staging and discussion in a multidisciplinary team.
Level of evidence: III
Strength of recommendation: C

15. which patients should be offered ART following radical prostatectomy?

ART is radiotherapy after RP for patients without evidence of disease (including an undetectable PSA) but who are at high risk of tumor progression, such as those with pT3 tumors with or without positive surgical margins (R1). Three randomized phase III trials led by the South Western Oncology Group (SWOG), the EORTC and the German Cancer Society Arbeitsgemeinschaft Radiologischer Onkologie (ARO) demonstrated a nearly 20% absolute benefit for biochemical progression-free survival (bNED) after ART (60–64 Gy) compared with a 'wait and see' policy, mostly for pT3 cN0 or pN0 tumors. The greatest benefit (30% bNED after 5 years) was seen in patients with positive margins and pT3 tumors [154–156]. The 10-year follow-up of the EORTC trial confirmed these results [157]. In the SWOG prospective study, OS improved from 13.5 years without to 15.2 years with ART [156]. The EORTC trial central pathological review showed that the treatment benefit in patients with negative margins did not remain significant. The HR was 0.87 ($P = 0.601$) with negative surgical margins and 0.38 ($P < 0.0001$) with positive surgical margins [158]. However, this was a subgroup analysis. Therefore, the results must be interpreted with caution. This benefit was also seen in the real adjuvant situation, with an undetectable PSA before the start of RT [76]. In the ARO trial,

159 patients with undetectable PSA were randomized into the observation and 148 into the adjuvant irradiation arm (60 Gy in 30 fractions over 6 weeks). After a median follow-up of nearly 5 years, biochemical control was significantly improved by ART: 72% versus 54% ($P < 0.03$). In the subgroup of pT3 R1 tumors, the absolute advantage in biochemical control rose from 18% to 28% [76].

It is known that the extent and multifocality and to a lesser extent the location of surgical margins are significant predictors of biochemical progression after RP. In a retrospective series of 7160 patients treated with RP including 1540 patients with positive margins, the 7-year progression-free probability was 60% in those patients, resulting in an HR for biochemical recurrence of 2.3 in the case of positive surgical margins compared with negative margins. There was also an increased risk of biochemical recurrence in patients with multiple versus solitary positive surgical margins (HR 1.4) and extensive versus focal positive surgical margins (adjusted HR 1.3) [159]. From the data of the randomized trials mentioned above, patients with positive margins and pT3 tumors do stand to profit most from postoperative radiation therapy. It may also be that that tumor grade, especially grade at the margin, affect risk of recurrence [160–162] and hence the potential to gain from ART.

A weakness of these trials is that the control arms did not routinely have radiotherapy on early evidence of PSA relapse a question being addressed in current trials such as RADICALS. The possible benefit of ART must be weighed carefully in consideration of potential long-term side-effects. However, with modern treatment techniques, the rate of severe side-effects is low.

Recommendation 15: Patients with positive surgical margins or extracapsular extension after RP should be informed about the pros and cons of ART.
Level of evidence: I
Strength of recommendation: A

16. should radical treatment be applied when positive nodes are found at lymphadenectomy?

There are no randomized studies addressing the efficacy of local treatment (radiotherapy or RP) in the N+ population. The retrospective data show an OS benefit for RP in N+ patients [163]. The authors analyzed 688 patients with RP and 250 without RP. There was an imbalance in the number of positive lymph nodes: 17.2% with RP had ≥4 positive nodes versus 28% in the patient group without RP. In the multivariate model, RP was a strong independent predictor of survival (HR 2.04). OS from N+ patients who are treated with ADT alone in this study was reported to be 28.2% at 10 years. Schröder et al. [164] also reported poor 10-year OS rates of well below 30% in EORTC 30846 (randomizing between immediate and deferred ADT in patients with locally advanced and N1 prostate cancer having no radical local treatment). These results were in contrast with studies on N1 disease in which ADT has been combined with local radiotherapy or RP. A small trial ($n = 98$) recruiting between 1988 and 1993 tested immediate adjuvant ADT versus ADT at time of symptoms or metastasis in patients who were treated with RP and in whom pathologically involved lymph nodes were found [165]. Patients treated with immediate ADT had, with a median follow-up of 12 years, a significantly better OS than patients treated with deferred ADT (76% versus 53%) [165]. It must be noted that 25% (13 of 51) patients randomized to deferred ADT had not started ADT after a median follow-up of >11 years. This small trial started in the pre-PSA era and only a limited lymph node dissection was carried out. Therefore, the results may not apply to current patients with minimal involvement of one or two nodes after an extended dissection.

On balance, the survival evidence favoring immediate adjuvant hormone therapy in pN1 patients is not strong enough to make this therapy a requirement in all patients and a reasonable alternative in those with limited nodal disease is close monitoring. A clinically relevant benefit of immediate ADT has only been suggested in N1 patients if they also had local treatment (RP or radiotherapy) [166].

The addition of external beam RT after RP in patients with histologically proven lymph node metastases remains controversial. There are some retrospective data supporting its use in selected cases. Da Pozzo et al. [49] reported on a retrospective series of 250 patients with proven pN+ following RP. One hundred twenty-nine patients (51.6%) were treated with a combination of RT and HT, while 121 patients (48.4%) received adjuvant HT alone. With a median follow-up of 91 months, the biochemical specific survival and CSS rates at 10 years were 53% and 80%, respectively. In a multivariate analysis, adjuvant RT and the number of positive nodes were independent predictors of BCR-free survival ($P = 0.002$ and $P = 0.003$) as well as of CSS ($P = 0.009$ and $P = 0.01$) [49]. Briganti et al. [167] carried out a matched pair analysis between a group of N+ patients after RP who received ADT versus patients who received the same treatment and additional radiotherapy to the prostatic bed and pelvis. The analysis is based on a subset of 364 patients with lymph node involvement out of a total of 703 patients. With a median follow-up of 95 months, the addition of radiotherapy appeared to improve cancer specific and OS. Limitations of the analysis include the retrospective nature, the lack of standardization of radiotherapy and ADT and the lack of pathology review [167].

Recommendation 16a: Radical locoregional therapy is recommended for N1 M0 patients suitable for an aggressive management approach.
Level of evidence: III
Strength of recommendation: B/C
Recommendation 16b: RT added to ADT is not standard treatment in pN+ patients after RP but may be considered in selected cases.
Level of evidence: IV
Strength of recommendation: C
Recommendation 16c: pN1 patients after RP who are judged to have a high risk for progression should receive immediate ADT.
Level of evidence: II
Strength of recommendation: B/C

17. what is the management of non-metastatic castration-resistant prostate cancer?

At baseline, serum testosterone, a bone scan and a pelvic-abdomen CT scan are recommended. M0 castration resistant prostate cancer (CRPC) is defined if these imaging procedures are normal and if serum testosterone measurement is <0.50 ng/ml. Approximately one-third of patients with M0 CRPC develop metastases within 2 years. A high PSA and a rapidly rising PSA are the two main risk factors for metastases [168]. Preliminary data about axial skeleton MRI suggest higher sensitivity compared with bone scan [169]. No sufficient data are available about choline-PET or fluoride-PET assessments in patients with CRPC M0. Imaging procedures are recommended during follow-up only if the results would change treatment management, or in case of symptoms.

Although there is no available randomized study, it is generally agreed that patients with PSA progression despite castration should continue with life-long ADT. Subsequent hormonal manipulation may be used as a choice of treatment in patients progressing on castration. The second-line endocrine treatment options include the addition of an androgen receptor inhibitor (antiandrogen), antiandrogen withdrawal, estrogen, ketoconazole and steroids. No strict recommendation can be made with respect to the most effective drug to be used for secondary hormonal manipulation since data from randomized trials are lacking. There are no data showing OS benefit, increased cancer-specific survival or progression-free survival benefit from secondary endocrine treatment in these patients.

In a phase III trial, 1432 patients with CRPC M0 with high risk for bone metastases (PSA >8 ng/ml and/or PSA doubling time of ≤10 months) were randomly assigned to denosumab or placebo. Denosumab significantly increased bone-metastasis-free survival by a median of 4.2 months compared with placebo [median 29.5 (95% CI 25.4–33.3) versus 25.2 (22.2–29.5) months; HR 0.85, 95% CI 0.73–0.98, $P = 0.028$]. Thirty-three (5%) patients on denosumab developed osteonecrosis of the jaw (ONJ) versus none on placebo. No OS difference was detected [170]. The efficacy/toxicity balance should be discussed with the patient, as well as the duration of treatment (several years with a monthly subcutaneous injection) if denosumab is used in this setting.

There are no data supporting the use of chemotherapy in patients with CRPC M0. New drugs such as CYP17 inhibitors, MDV3100 (enzalutamide), sipuleucel-T and taxanes, have not been reported in the context of a randomized trial for CRPC M0 patients.

Recommendation 17a: Patients with CRPC should continue with life-long ADT.
Level of evidence: V
Strength of recommendation: A
Recommendation 17b: In patients who progress on androgen deprivation, second-line HTs can include the addition of an androgen receptor inhibitor (antiandrogen), antiandrogen withdrawal, estrogen, ketoconazole or steroids.
Level of evidence: III
Strength of recommendation: B
Recommendation 17c: Patients with CRPC M0, evidence of local progression, and no possibility for local treatment shall be managed like patients with CRPC M1 disease.
Level of evidence: V
Strength of recommendation: B

18. what standard treatment should be used in metastatic hormone-naive prostate cancer?

Metastatic hormone-naive prostate cancer is defined by disease with dissemination to the bones, visceral sites or lymph nodes outside the pelvis, detected by imaging procedures in a patient who is not receiving endocrine manipulation for his prostate cancer. The standard of care consists of immediate castration (also called ADT) using either LHRH agonist, LHRH antagonist or a bilateral orchidectomy. These treatment options have similar efficacy [171–174]. If an LHRH agonist is chosen for ADT, an antiandrogen should be used concomitantly during the first 3–4 weeks to prevent a testosterone flare. In a patient at high risk for immediate major complication from metastases (e.g. spinal cord compression), an immediate LHRH agonist should be avoided, and other options including bilateral orchiectomy, antiandrogen monotherapy and LHRH antagonist are standard initial treatments.

No clinically relevant survival advantage was demonstrated for combined androgen blockade (CAB) over castration alone using various antiandrogens [175, 176]. Insufficient data are available regarding the use of bicalutamide in CAB [177]. Inferior survival results were shown comparing single-agent androgen receptor inhibitor (bicalutamide) to castration [178]. Insufficient published data are currently available with the use of intermittent ADT instead of continuous ADT for metastatic prostate cancer [94, 179], thus restricting its use to patients with severe intolerance to continuous ADT. No survival advantage was reported with the addition of nontaxane chemotherapy to ADT in metastatic hormone-naive prostate cancer [180]. No phase III data are currently available regarding the use of taxanes in this setting. In patients with bone metastases from hormone-naive prostate cancer, only limited phase III data are available regarding the use of bone-targeted agents. Specifically, no data are available regarding the use of zoledronic acid or denosumab. One phase III trial testing oral clodronate reported long-term survival advantage, although interpretation of the data is difficult [181].

Monitoring of patients receiving ADT for metastatic hormone-naive prostate cancer should include clinical assessment and PSA measurement, as well as recording and managing side-effects. Although initial imaging by bone scan and CT scan (or MRI) of the abdomen and pelvis is strongly recommended, a systematic imaging surveillance is not mandatory in absence of a PSA rise or cancer-related symptoms. PSA is not always a reliable indicator of disease activity in the rare population of patients with undifferentiated (or anaplastic) metastatic prostate cancer (often with neuroendocrine features, predominant visceral metastases or

osteolytic phenotype): a more systematic imaging policy should be considered in these patients.

Recommendation 18a: Immediate continuous castration is the preferred treatment option for metastatic hormone-naïve prostate cancer.
Level of evidence: I
Strength of recommendation: B
Recommendation 18b: An antiandrogen should be given for 3–4 weeks when starting androgen deprivation with an LHRH agonist for metastatic hormone-naïve prostate cancer, to counteract testosterone flare.
Level of evidence: III
Strength of recommendation: B
Recommendation 18c: IAD is not recommended for metastatic hormone-naïve prostate cancer outside of a trial, unless there is significant intolerance of hormone therapy.
Level of evidence: I
Strength of recommendation: C
Recommendation 18d: Concomitant bone-targeting therapy with either denosumab or a bisphosphonate is not recommended for metastatic hormone-naïve prostate cancer.
Level of evidence: II
Strength of recommendation: C
Recommendation 18e: Concomitant cytotoxic chemotherapy is not recommended for metastatic hormone-naïve prostate cancer outside a clinical trial.
Level of evidence: II
Strength of recommendation: D

19. what are the treatment options in patients with metastatic CRPC?

As for M0 CRPC, it is recommended to use continuous ADT in patients with M1 CRPC. Standard treatment of patients with metastatic CRPC is docetaxel-based chemotherapy with an OS benefit in two phase III studies [182, 183]. The recommended regimen is docetaxel–prednisone three times weekly. As the OS gain in the subgroups of asymptomatic (or minimally symptomatic) and symptomatic patients is similar [184], treatment with docetaxel can be deferred in asymptomatic patients. Early docetaxel may be considered in asymptomatic patients with either a rapidly rising PSA, especially after short-term response to ADT (since these patients are likely to be soon symptomatic), patients with visceral metastases and patients with anaplastic prostate cancer.

OS benefit, but no PFS benefit, has been shown in patients with asymptomatic CRPC in two phase III trials with sipuleucel-T [185, 186]. These patients should have a good performance status (0 or 1) and no visceral disease. These trials have been criticized for their control arm (leucopheresis) depleting patients of leukocytes, with the OS benefit being apparently restricted to patients >65 years [187]. The treatment is not openly available in Europe.

An option for asymptomatic patients who are not treated with docetaxel is participation in a clinical trial. If there is no suitable trial available, secondary hormonal therapies can be used such as administration of antiandrogens, antiandrogen withdrawal, steroids, ketoconazole or estrogens. The responses to these manipulations are mostly PSA responses and in general are short lived. None of these agents have been shown to have an OS benefit. Phase I/II studies of abiraterone acetate in chemotherapy-naive patients with asymptomatic CRPC have shown impressive response rates [188–190]. A phase III trial for asymptomatic or minimally symptomatic patients before docetaxel chemotherapy has completed accrual, and the results are awaited (NCT00887198).

Recommendation 19a: Docetaxel chemotherapy is appropriate for symptomatic patients with metastatic castration-resistant disease and good performance status, and should also be discussed with asymptomatic patients with evidence of rapidly progressing disease.
Level of evidence: I
Strength of recommendation: B
Recommendation 19b: Second-, third- and fourth-line hormone manipulations are options to seek short-term responses.
Level of evidence: III
Strength of recommendation: B

20. are there any effective anticancer treatments for those who have failed docetaxel?

Resistance to docetaxel has not been well defined. Early (<12 weeks) PSA increases after start of docetaxel therapy should be ignored when determining progression [191]. Data from several phase III trials in patients progressing under or after treatment with docetaxel are now available. Survival benefit has been shown for cabazitaxel, abiraterone, radium-223 and MDV3100 (enzalutamide) [192–195]. The radium-223 phase III trial restricted its inclusion criteria to patients with symptomatic bone metastases (without visceral metastases) and included patients who were never going to have docetaxel. It demonstrated both symptomatic and survival benefit.

There are no predictive factors up to now to decide for an individual patient which treatment is the preferred second-line treatment after docetaxel. Choice can be based on clinical considerations, including the patient's characteristics and preferences. The sequential or combined use of these new agents needs to be investigated.

If the new treatments are not available retreatment with docetaxel is an option [196–198] for patients who have responded to first-line docetaxel and who have not progressed while on docetaxel. Mitoxantrone with prednisone [192, 199] can be used for short-term palliation of symptoms.

Recommendation 20a: Patients with good performance status should have discussion about further anticancer treatment if one of the following is available: cabazitaxel, abiraterone, MDV3100 (enzalutamide), radium-223.
Level of evidence: I
Strength of recommendation: A
Recommendation 20b: Patients with good performance status should have discussion about retreatment with docetaxel or second-line chemotherapy with mitoxantrone if they had

responded well to previous chemotherapy, unless new effective lower-toxicity agents are available.
Level of evidence: III
Strength of recommendation: C

21. should an antiosteoclastic drug be used in patients with castration-resistant prostate cancer and bone metastases?

The RANK-ligand inhibitor, denosumab, and the bisphosphonate, zoledronic acid, have been shown to prevent or delay skeletal-related events (SREs) in patients with bone metastases from CRPC [200, 201]. Denosumab was shown to be superior to zoledronic acid in preventing SREs [201]. Zoledronic acid is contraindicated in patients with creatinine clearance <30 ml/min. For less potent bisphosphonates, no benefit was shown in phase III trials testing pamidronate; one modestly sized trial suggested a survival benefit for Clodronate [191]. No trial correctly addressed the question of early versus late administration of denosumab or zoledronic acid. Tumor burden (e.g. >3 bone mets, high alkaline phosphatase) and anatomic site of bony metastases as well as previous history of SRE can be used to judge SRE risk. The optimal duration to administer these agents is unknown.

In a large phase III trial [201], median time to first SRE was 2.07 months with denosumab compared with 17.1 months with zoledronic acid (HR 0.82, 95% CI 0.71–0.95; $P = 0.0002$ for non-inferiority; $P = 0.008$ for superiority). More hypocalcemia events occurred in the denosumab group (13%) than in the zoledronic acid group (6%). ONJ occurred infrequently (2% versus 1%). No difference in OS was observed.

Only limited data about the efficacy/toxicity profile when switching between these agents are available. In a phase II trial, 50 patients with increased urinary N-terminal telopeptide (NTx) levels (a bone resorption marker) despite prior zoledronic acid treatment were randomized to either continue on bisphosphonates or receive subcutaneous denosumab. Denosumab normalized NTX levels more frequently than continuing bisphosphonate treatment, and a lower proportion of patients in the denosumab group experienced SREs (71% versus 29%; $P < 0.001$) [202].

Oral calcium and vitamin D are strongly recommended when using either denosumab or zoledronic acid. Before each administration of zoledronic acid, renal function test and serum calcium level should be evaluated. Serum calcium should be measured before each denosumab injection. A baseline dental evaluation is mandatory before initiating denosumab or zoledronic acid; during follow-up, a close monitoring of oral conditions is strongly recommended to detect early ONJ. Prevention of ONJ may include prophylactic use of antibiotics in patients requiring invasive dental care.

Recommendation 21a: In patients with bone metastases from CRPC at high risk for clinically relevant SREs, denosumab or zoledronic acid can be recommended, and a large trial found that denosumab delayed SREs for longer than zoledronic acid. Neither agent has been shown to prolong survival.
Level of evidence: I
Strength of recommendation: B
Recommendation 21b: In patients with bone metastases from CRPC at high risk for clinically relevant SREs, neither clodronate nor pamidronate have been shown to have palliative benefit.
Level of evidence: I
Strength of recommendation: E
Recommendation 21c: Patients on antiosteoclastic drugs should have monitoring of serum calcium and oral health; patients on zoledronate additionally require monitoring of renal function.
Level of evidence: II
Strength of recommendation: A

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disclosure

Dominik Berthold (advisory board role—Astellas, Sanofi, Janssen); Gedske Daugaard (advisory board role—Sanofi-Aventis, Janssen); David Dearnaley ('reward for inventions' for abiraterone o and advisory board role—Amgen, Takeda, Novartis, AstraZeneca, institution (ICR) receives royalties from the drug abiraterone and department has research collaboration with Algeta); Karim Fizazi (research and speaker's bureau—Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen, Astellas/Medivation, Novartis, Sanofi-Aventis, Dendreon, Bayer, Keocyt, Millennium-Takeda, Orion, Merck, Exelixis); Silke Gillessen (advisory board role—Millennium, Janssen, Sanofi); Alan Horwich (no personal conflicts, institution (ICR) receives royalties from the drug abiraterone and department has research collaboration with Algeta); Jonas Hugosson (lecture fees from Abbott Pharmaceuticals, GlaxoSmithKline, Lilly Pharmaceuticals); Vesa Kataja (conducting research on cabazitaxel—Sanofi and abiraterone—Janssen); Maciej Kwiatkowski (consulting GlaxoSmithKline); Anwar Padhani (speaker's bureau—Janssen); Chris Parker (advisory board role—Amgen, Bayer, Bristol-Myers Squibb, Dendreon, Janssen and Takeda and department has research collaboration with Algeta); Thomas Wiegel (advisory board role—Takeda, Novartis, Ipsen, AstraZeneca, Hexal, Jansen, Bayer).

appendix

Members of the Panel

Dr. Chris Parker was unable to attend the conference, but had a major impact on the preparatory work for the conference and on the final manuscript.

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