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Contemporary Role of Androgen Deprivation Therapy for Prostate Cancer

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Abstract

Context—Androgen deprivation therapy (ADT) for prostate cancer (PCa) represents one of the most effective systemic palliative treatments known for solid tumors. Although clinical trials have assessed the role of ADT in patients with metastatic and advanced locoregional disease, the risk–benefit ratio, especially in earlier stages, remains poorly defined. Given the mounting evidence for potentially life-threatening adverse effects with short- and long-term ADT, it is important to redefine the role of ADT for this disease.

Objective—Review the published experience with currently available ADT approaches in various contemporary clinical settings of PCa and reported serious treatment-related adverse events. This review addresses the level of evidence associated with the use of ADT in PCa, focusing upon survival outcome measures. Furthermore, this paper discusses evolving approaches targeting androgen receptor signaling pathways and emerging evidence from clinical trials with newer compounds.

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Evidence acquisition—A comprehensive review of the literature was performed, focusing on data from the last 10 yr (January 2000 to July 2011) and using the terms androgen deprivation, hormone treatment, prostate cancer and adverse effects. Abstracts from trials reported at international conferences held in 2010 and 2011 were also evaluated.

Evidence synthesis—Data from randomized controlled trials and population-based studies were analyzed in different clinical paradigms. Specifically, the role of ADT was evaluated in patients with nonmetastatic disease as the primary and sole treatment, in combination with radiation therapy (RT) or after surgery, and in patients with metastatic disease. The data suggest that in men with nonmetastatic disease, the use of primary ADT as monotherapy has not shown a benefit and is not recommended, while ADT combined with conventional-dose RT (<72 Gy) for patients with high-risk disease may delay progression and prolong survival. The postoperative use of ADT remains poorly evaluated in prospective studies. Likewise, there are no trials evaluating the role of ADT in patients with biochemical relapses after surgery or RT. In patients with metastatic disease, there is a clear benefit in terms of quality of life, reduction of disease-associated morbidity, and possibly survival. Treatment with bilateral orchiectomy, luteinizing hormone–releasing hormone agonist therapy, with and without antiandrogens has been associated with various serious adverse events, including cardiovascular disease, diabetes, and skeletal complications that may also affect mortality.

Conclusions—Although ADT is an effective treatment of PCa, consistent long-term benefits in terms of quality and quantity of life are predominantly evident in patients with advanced/metastatic disease or when ADT is used in combination with RT (<72 Gy) in patients with high-risk tumors. Implementation of ADT should be evidence based, with special consideration to adverse events and the risk–benefit ratio.

Keywords

Prostate cancer; Androgen deprivation; Hormone treatment; Adverse effects

1. Introduction

Currently, <5% of men with newly diagnosed prostate cancer (PCa) have distant metastases at first presentation, compared with 20–25% >20 yr ago [1]. Despite this, the use of androgen deprivation therapy (ADT) increased sharply between 1989 and 2001 [2], which suggests that many patients without evidence of distant metastases receive ADT not always according to evidence-based indications. Data from randomized controlled trials (RCTs) and contemporary population-based cohorts suggest that ADT contributes to significant morbidity and potentially to an increase in the risk of mortality in patients undergoing long-term treatment [3–6]. For the purpose of this collaborative effort, a comprehensive review of the contemporary literature was conducted in the following clinical paradigms: nonmetastatic disease (as primary and sole treatment modality, in combination with local treatments, and at the time of biochemical relapse) and metastatic disease. In addition, data were reviewed regarding different endocrine treatment approaches and treatment-related morbidity and mortality. The goal was to focus on evidence-based information that may be useful for daily urologic-oncologic clinical practice.

2. Evidence acquisition

A comprehensive PubMed and Web of Science search was performed using the terms androgen deprivation, hormone treatment, prostate cancer, and *adverse effects*, and preference was given to articles published in English within the last 10 yr. Studies were selected based on clinical relevance, and analysis was limited to RCTs and population-based studies, with very few exceptions. Additional references were extracted from selected

review articles; also evaluated were supplemental abstracts from trials reported at 2010 and 2011 annual meetings from the European Association of Urology, American Urological Association, American Society of Clinical Oncology, and American Society for Radiation Oncology.

3. Evidence synthesis

3.1. Androgen deprivation therapy for nonmetastatic disease

3.1.1. Androgen deprivation therapy alone compared with local standard of care

3.1.1.1. Androgen deprivation therapy alone compared with observation: Two population-based studies separately analyzed the Surveillance Epidemiology and End Results Medicare database to compare primary ADT (treatment started 6 mo after PCa diagnosis) with watchful waiting among men with cT1–cT2 PCa [7,8]. Although two distinct statistical methods were used to reduce imbalances related to the nonrandomized nature of these studies, survival did not appear to be significantly different between the two groups. In one of the reports [8], a nonsignificant benefit for cancer-specific survival (CSS) was found in men with poorly differentiated PCa.

Although treating a patient with bicalutamide alone may not be considered standard ADT, results from the Early Prostate Cancer (EPC) program further discourage the primary use of endocrine treatment in clinically localized disease. This trial was designed to define the role of daily bicalutamide 150 mg in addition to standard treatment of localized or locally advanced M0 disease. Three different groups of patients (based on the primary treatment used: radical prostatectomy [RP], radiation therapy [RT], or watchful waiting) were randomized to receive placebo or bicalutamide. Among the 2285 patients under watchful waiting, 71% had cT1–cT2 disease, whereas the remaining patients had locally advanced disease. In both cases, at a median follow-up of 7.4 yr, overall survival (OS) was not improved in men receiving bicalutamide compared with placebo [9] (Table 1).

3.1.1.2. Androgen deprivation therapy with or without radiation therapy: Two studies compared primary ADT alone with RT plus ADT (Table 1). SPCG-7/SFUO-3 was a phase 3 RCT focusing on men with cT1–cT4N0 disease, in which the ADT plus RT arm showed a clear reduction in mortality compared with the ADT alone arm [10]. Similarly, the results of the CAN-NCI-C-PR3 study, in which men with high-risk M0 disease were randomized either to ADT alone or to RT and ADT, have been presented [11]. The overall risk of death was significantly lower for patients with locally advanced or high-risk disease treated with RT plus ADT (overall benefit, 23%), and CSS was improved as well (overall benefit, 43%). The results of both trials support the hypothesis that adding RT to ADT improves survival compared with ADT alone in patients with high-risk nonmetastatic PCa [10,11]. A third trial comparing 3 yr of ADT with or without RT in 263 men with cT3–cT4 PCa showed a clear benefit in terms of 5-yr progression-free survival (PFS) and 5-yr metastasis-free survival in favor of the combined arm [12]. Long-term results are awaited.

3.1.1.3. Androgen deprivation therapy alone compared with surgery: Androgen deprivation has been compared with RP in node-positive patients [13–16]. Although a survival advantage for surgery over primary ADT was shown, these data are retrospective, and no RCTs have been designed to support this finding.

3.1.2. Radiation therapy plus androgen deprivation therapy compared with radiation therapy alone

3.1.2.1. Clinical evidence from randomized controlled trials: Several RCTs have shown a significant clinical benefit when short- or long-term ADT is combined with RT (Table 2) [17–25]. Various clinical factors, such as pretreatment prostate-specific antigen (PSA), Gleason score, and clinical T stage, may further define the relative benefits of short- or long-term ADT in patients treated with the combined approach. The risk stratification classification reported by D'Amico et al, which is used in most studies in men with clinically localized PCa, includes three distinct groups of patients: low risk (cT1–cT2a, Gleason score 2–6, PSA <10 ng/ml), intermediate risk (cT2b, Gleason score 7, PSA 10.1–20 ng/ml), and high risk (cT2c or Gleason score 8–10, or PSA >20 ng/ml) [26].

3.1.2.2. Low- and intermediate-risk patients (cT1–cT2b, Gleason score 2–7, PSA <20 ng/ml): Definitive results from the Radiation Therapy Oncology Group (RTOG) 9408 trial have recently helped clarify the role of ADT combined with contemporary doses of radiation for patients with low-risk PCa [22]. In this trial, 1979 men with low- to intermediate-risk PCa (cT1b–cT2b and PSA ≤20 ng/ml; only 9% of the total cohort also had Gleason score 8–10) were randomized to whole-pelvic RT alone (66.6 Gy) or combined with 4 mo of ADT, starting 2 mo before RT. At a median follow-up of 9.2 yr, an OS benefit at 10 yr was shown in the entire cohort of men receiving ADT plus RT compared with men treated with RT alone (62% vs 51%, $p = 0.03$) [22]. A post hoc analysis, although unplanned at the time of study design, was performed to define which risk categories could gain an advantage from the combined approach. Although a benefit in biochemical failure rates was seen in low-risk patients (35% of the total population), the survival advantage (OS and cancer-specific mortality [CSM]) pertained only to intermediate-risk patients who received ADT and RT [22]. Retrospective analyses from other large trials have also failed to demonstrate a survival benefit of combining ADT and RT in low-risk patients despite significant differences in disease-free survival in favor of the combined approach [27,28]. Thus, the routine use of ADT in low-risk patients should be discouraged at this time.

The combination of conventional-dose RT (<72 Gy) with short-term ADT in patients with intermediate-risk disease has been reported to improve local control and survival. As already discussed, subgroup analysis from the RTOG 9408 trial has shown that patients with intermediate-risk disease (54% of the total population) have a survival benefit (OS and CSM) and better biochemical failure rates when treated with short-term ADT and RT combined [22]. D'Amico et al. [29] reported the results of a randomized trial in 206 patients with intermediate- to high-risk organ-confined disease (15% had a Gleason score >7) treated with either 6 mo of luteinizing hormone–releasing hormone (LHRH) agonists plus RT (70–72 Gy) or with RT alone. Although median follow-up was short (7.6 yr), a significant benefit in OS and CSS was shown for the group receiving combined-modality treatment. Crook et al. [19] reported the results of a Canadian study of 378 men randomized to either 3 or 8 mo of neoadjuvant ADT plus RT (66 Gy). No differences were seen in the failure rates (biochemical, local, or distant) for the overall population; however, a trend toward improved disease-free survival (but not survival) favoring longer ADT was noted in high-risk patients (57% of the entire cohort).

The role of ADT in combination with higher doses of RT (>72 Gy) has never been explored prospectively in intermediate-risk patients. Nonetheless, critical trials are ongoing and may provide more definitive answers: RTOG 9910 is comparing 8 and 28 wk of neoadjuvant and concurrent ADT plus RT, and RTOG 0815 is evaluating more modern, high-dose radiation methods in combination with ADT.

3.1.2.3. High-risk patients (cT2c, Gleason score 8–10, PSA >20 ng/ml): Several RCTs support the combination of ADT and RT in patients with high-risk or node-positive PCa. In fact, patients for whom bilateral orchiectomy or a long-term course of ADT was combined with conventional-dose RT (65–70 Gy) have often been compared with men receiving RT alone (Table 2) [18,20,21,23,25]. A recent meta-analysis was conducted to study the impact of this combination on a number of outcome measures [30]. Patients treated with ADT plus RT had a significant reduction in the risk of local recurrence and an overall benefit in biochemical failure and clinical PFS. Combination therapy also resulted in a 5.5% and 4.9% reduction in cancer-specific and overall mortality, respectively [30].

Analysis of two European Organization for Research and Treatment of Cancer (EORTC) trials may raise some considerations regarding the optimal duration of hormone treatment in patients with locally advanced PCa. In EORTC trial 22863, patients received RT (70 Gy) either alone or combined with 3 yr of ADT. The OS difference among the two groups was 20% at both 5 and 10 yr [18,31]. Given this survival advantage, a second trial, EORTC 22961, was designed, in which all patients undergoing RT (70 Gy) received ADT for either 6 mo or 3 yr; no patients were treated by RT alone. Although a benefit in CSS was found for patients undergoing long-term ADT (hazard ratio [HR]: 1.71; 95% confidence interval [CI], 1.14–2.57; $p = 0.002$), the 4% difference in 5-yr OS in favor of the long-term treatment was not significant [17]. Likewise, in the RTOG 9202 trial, all patients undergoing RT were randomized to receive either 4 mo of neoadjuvant and concurrent ADT or 4 mo plus an additional 2 yr of adjuvant ADT. At 10 yr, all outcome measures were improved in the long-term arm, with the exception of OS (51.6% vs 53.9%, $p = 0.36$). Interestingly, when analysis was restricted to Gleason score 8–10 cancers, better OS was documented in the long-term arm ($p = 0.0061$) [32]. As a hypothesis, RCTs comparing short- and long-term ADT plus RT suggest that a few months of neoadjuvant and concomitant hormone therapy may be as effective as 3 yr in patients with less advanced disease, as opposed to patients with high-risk PCa (specifically, Gleason score 8–10), in whom long-term ADT may be more effective. Additional studies are needed to determine the optimal duration of ADT in combination with RT in the various risk groups treated.

The most appropriate extent of the radiation field (prostate with or without pelvic nodes) also requires further study. Although RTOG 9413 was designed to compare the combination of ADT and whole-pelvic RT with the combination of ADT and prostate RT only in patients with intermediate- and high-risk PCa, the trial can be considered only hypothesis generating [33]. Finally, several investigators have raised the question of the beneficial role of ADT when higher radiation doses are delivered [34–36]; GETUG 18, a French RCT, is currently randomizing high-risk patients to long-term ADT plus either 70 or 80 Gy and may help answer this question.

3.1.3. Androgen deprivation therapy given as an adjuvant after local therapy—

The role of immediate androgen deprivation for patients at high risk for recurrence after local treatment, as opposed to treatment at any other time in the future, also remains unresolved. Long-term survival figures have been reported in patients with biochemical relapse after RP treated with ADT deferred at the time of development of metastatic disease [37,38]. The limited data regarding the most appropriate timing of ADT in early-disease patients or patients who have biochemically relapsed are discussed below and illustrated in Table 3.

3.1.3.1. Androgen deprivation therapy in locally advanced and node-positive patients: One study that has largely influenced clinical practice in the last decade is the Eastern Cooperative Oncology Group (ECOG) 3886 trial [39,40]. Patients who underwent RP and had pathologic evidence of nodal involvement were randomized to either immediate

postoperative or deferred (at the time of bone metastases) ADT. With a median follow-up of 11.9 yr, the trial showed a significant improvement in OS ($p = 0.04$) and CSS ($p < 0.0001$) in favor of the patients receiving ADT immediately after surgery [39,40]. The study, however, raised several concerns [41], such as the small sample size (98 men from 36 centers), the lack of a central pathologic review to assess stages and Gleason scores, and the lack of baseline PSA testing. More recently, adjuvant endocrine therapy after surgery was evaluated as part of the EPC trial. Patients with locally advanced disease randomized to receive RP and bicalutamide (150 mg) did not show any survival benefit compared with men receiving placebo ($p = 0.51$). Compared with ECOG 3886, only 2% of patients had nodal involvement in this trial [42].

The EORTC conducted two RCTs to compare immediate and deferred ADT in patients with locally advanced PCa who did not receive local treatment. In EORTC 30846, all patients had documented nodal involvement. Deferred treatment was started at evidence of either clinical or PSA recurrence. While the study did not show a survival difference between the two arms, it was considered underpowered to adequately test the hypothesis [43]. In EORTC trial 30891, 989 patients had nodal disease in only 5% of the cases and were enrolled because they were unable or unwilling to receive a potentially curative treatment. Deferred ADT was started only at the time of clinical progression. The study showed a small difference in OS in favor of immediate ADT; however, CSS was similar [44]. Among patients in the deferred arm, a PSA doubling time (DT) <12 mo was the strongest predictor of death [45].

3.1.3.2. Androgen deprivation therapy at biochemical relapse: Approximately 30–40% of men undergoing surgery with curative intent demonstrate evidence of biochemical recurrence (BCR; ie, PSA recurrence) [37]. While a proportion of these patients may be salvaged by RT, the most appropriate systemic approach remains elusive at this time. According to retrospective series, these patients may have long survival, even when ADT is delayed until evidence of metastases [37,38]. In a matched comparison of patients experiencing BCR after surgery, Siddiqui et al. [46] could not find significant survival differences among patients starting ADT at different times after BCR; CSS was slightly improved ($p = 0.009$), but OS was not ($p = 0.427$), in patients who received ADT immediately after surgery compared with patients starting at the time of systemic progression. In a similar retrospective study of 1352 men who had BCR, only higher-risk patients (Gleason score >7 and PSA DT ≤12 mo) benefited from early ADT, which delayed clinical metastases (HR: 2.12; $p < 0.01$) [47]; however, a survival benefit was not documented.

From these studies, there is no consensus at the present time regarding the optimal management of patients with BCR after surgery and/or RT.

3.1.3.3. Salvage radiation therapy and androgen deprivation therapy combined: Two large RCTs investigated the role of adjuvant RT in patients at high risk for failure after RP [48,49]. Although significant improvements in biochemical PFS and clinical PFS were reported in both trials, an OS benefit was observed in only one case [49], further inspiring prospective studies on the role of a combined (ADT plus RT) salvage approach. In RTOG 9601, 771 patients experiencing BCR after surgery were randomized either to RT alone (64.8 Gy) or to RT combined with 2 yr of concomitant and adjuvant bicalutamide 150 mg [50]. At a median follow-up of 7.1 yr, freedom from PSA progression ($p < 0.0001$) and the incidence of metastases ($p < 0.04$) were improved by bicalutamide. Longer follow-up is required for the OS analysis. Additional trials are accruing patients for whom the role of ADT combined with postoperative RT will be further elucidated. Specifically, RTOG 0534 will compare three treatment arms: RT alone (64.8–70.2 Gy), RT plus ADT (4–6 mo), and

whole-pelvic RT plus ADT (4–6 mo). Likewise, the Radiotherapy and Androgen Deprivation in Combination after Local Surgery trial will compare RT alone (52.5–66.0 Gy), RT plus short-term ADT (6 mo), and RT plus long-term hormone therapy.

3.2. Androgen deprivation therapy in metastatic disease

There is little debate regarding the immediate need for ADT in patients diagnosed with metastatic PCa. In this setting, the risk of developing symptoms (bone pain, renal failure, anemia, pathologic fractures, spinal cord compression) can be reduced with early implementation of ADT [51]. The median survival time varies depending on disease burden and pain [52]; however, in contemporary patients, it is longer (7–181 mo), partly because of lead-time bias from early diagnosis [38] and the progress made in the treatment of castration-resistant PCa (CRPC). Selected trials are summarized in Table 4.

3.3. Treatment options and strategies

3.3.1. Gonadal androgen ablation

3.3.1.1. Surgical and medical castration: Bilateral orchiectomy causes rapid and sustained suppression of testicular androgens with resulting circulating testosterone levels <20 ng/ml in most patients [53]. Although free of compliance issues and apparently associated with good quality of life (QoL) [54], bilateral orchiectomy has been largely replaced by medical castration with LHRH agonists because of improved patient and physician acceptance. LHRH agonist formulations may differ in testosterone-suppression levels and duration of suppression [55]; however, no data relate these differences to differences in disease progression or survival.

3.3.1.2. Combined androgen blockade: In advanced and metastatic PCa, medical or surgical castration has often been combined with an antiandrogen. Despite many RCTs comparing combined androgen blockade (CAB) with castration alone, the role of CAB is still debated (Table 4)[56–59]. A large meta-analysis demonstrated that CAB reduced the risk of death by only 2% (8% when trials using cyproterone acetate were excluded; $p = 0.005$); however, the survival benefit was so small that CAB could not be widely recommended in clinical practice [60]. Moreover, the meta-analysis included trials in which a short-term antiandrogen was not used for disease-flare prevention. Exclusion of those trials from the meta-analysis, however, resulted in no difference in survival between CAB and castration [61]. In fact, when LHRH agonists are administered alone, the increase in circulating testosterone during the first week may cause a painful disease flare in patients with high-volume, symptomatic, bony disease (4–10% of M1 patients) [62]. This problem may be ameliorated by an oral nonsteroidal antiandrogen administered at least 2–7 d before starting the LHRH agonist [57,63].

3.3.1.3. Intermittent androgen deprivation: Intermittent androgen deprivation (IAD) is a treatment option that is often used outside clinical trials and practice guidelines. The goal behind IAD is improvement in QoL, prevention of complications related to long-term ADT, and delay of the castration-resistant state of PCa. Improvements in QoL have been evaluated [64,65] and actually show a very limited advantage regarding sexual function and impotence [66,67]. RCTs conducted thus far have not provided definitive information regarding the relative efficacy of this approach because of a variety of methodological issues related to relatively small and underpowered studies and nonuniform treatment schemas. Results of the National Cancer Institute of Canada PR7 trial were recently presented. A total of 1386 patients were randomized to IAD or to continuous ADT if a PSA >3.0 ng/ml was documented >1 yr after radical therapy for localized PCa. In the IAD arm, treatment was delivered for 8 mo, while restart during the time off treatment was dictated by a PSA rise

>10 ng/ml. In terms of OS (primary endpoint), the trial resulted in noninferiority of IAD (HR: 1.02; 95% CI, 0.86–1.21; noninferiority, $p = 0.009$) as compared with continuous treatment. Time to castration resistance (secondary endpoint) was improved on the IAD arm (HR: 0.80; 95% CI, 0.67–0.98; $p = 0.024$). Finally, there were no differences in adverse events, including myocardial events or osteoporotic fractures [68]. In metastatic PCa, the role of IAD is investigational pending the results of additional trials such as the Southwest Oncology Group trial 9346 (INT-0162).

3.3.2. Bicalutamide monotherapy—The role of bicalutamide within the EPC program has been discussed earlier [9,25,42]. Furthermore, three prospective RCTs have compared bicalutamide 150 mg with castration in locally advanced and metastatic disease [69–71]. In nonmetastatic patients, reported results are not considered sufficiently mature at this time, whereas a significant survival advantage for castration was seen in the M1 subgroup [71]. More recently, Tyrrell et al. [72] studied higher-dose bicalutamide (300, 450, and 600 mg) with regard to tolerability, pharmacokinetics, and clinical efficacy in M0 and M1 patients. Although survival resulted comparable to that for men receiving castration, larger series of patients are needed to confirm these data. The role of peripheral androgen blockade, produced by combining a 5α- reductase inhibitor with an androgen receptor (AR) antagonist, is currently being investigated. However, most studies are small and do not provide evidence of significant benefit.

3.3.3. Luteinizing hormone–releasing hormone antagonists—The principal mechanism of action of LHRH antagonists is competitive occupancy of the LHRH receptor. Unlike the LHRH agonists, LHRH antagonists cause an immediate and reversible suppression of luteinizing hormone and follicle-stimulating hormone secretion and, subsequently, testosterone [73,74]. Two LHRH antagonists have reached an advanced stage of clinical development and have recently entered the market: abarelix and degarelix. A phase 3 trial has shown that castration levels of testosterone are achieved faster than with leuprolide [73]. The relative effects on PFS and survival have not been reported. With regard to safety issues, abarelix's propensity to induce histamine release has caused potentially life-threatening systemic reactions and resulted in US Food and Drug Administration recall of its original approval in the United States [75].

Degarelix was tested against leuprolide in a phase 3 trial (study CS21) involving 610 men with PCa treated either with degarelix (240/80 or 240/160 mg) or monthly leuprolide at 7.5 mg. The study met its primary end point (noninferiority of degarelix in achieving and maintaining testosterone ≤0.5 ng/ml for 1 yr); in addition, testosterone and PSA declines were reported to occur significantly earlier with degarelix than with leuprolide ($p < 0.001$), while the side effect profiles were similar in both arms [76]. At present, degarelix is available as a monthly subcutaneous injection. Additional data in larger numbers of patients with long-term follow-up will help to better define the role of degarelix in the treatment of PCa.

3.3.4. Emerging hormonal approaches—Current evidence indicates that AR signaling remains active even with castration levels of serum testosterone (<50 ng/dl), contrary to the prior notion that disease progression after gonadal ablation necessarily implied androgen-independent escape mechanisms [77,78]. New insights into AR regulation have led to the development of novel compounds that have been, and are being, evaluated in clinical trials [77].

3.3.4.1. Cytochrome P450c17 inhibitors of steroidogenesis: Abiraterone acetate blocks the synthesis of androgens in the testes, adrenal glands, and prostate by inhibition of cytochrome P450c17, a rate-limiting enzyme in androgen biosynthesis. In phase 2

multicenter trials, abiraterone acetate, at a daily oral dose of 1000 mg, has shown promising clinical activity in patients with metastatic CRPC both before and after treatment with docetaxel [79,80]. Two phase 3 trials in patients with metastatic CRPC were conducted with abiraterone acetate in chemotherapy-naïve patients (COU-AA-302) and docetaxel-treated patients (COU-AA-301). COU-AA-301 resulted in an OS benefit of 35% and a median OS benefit of nearly 4 mo compared with placebo (HR: 0.65; 95% CI, 0.54–0.77; $p < 0.001$) [81]. Results of COU-AA-302 have not been reported at this time. TAK-700 is a selective oral inhibitor of the 17,20 lyase, which is a key enzyme in the production of steroidal hormones in the testes and adrenal glands. A phase 1/2 study revealed that at doses of 300 mg twice per day, TAK-700 was well tolerated by 26 patients with metastatic CRPC [82]. Phase 3 trials in patients with metastatic CRPC (chemotherapy treated and chemotherapy naïve) are in progress.

3.3.4.2. Second-generation androgen receptor antagonists: Compared with the first generation of nonsteroidal AR binders (flutamide, bicalutamide, and nilutamide), MDV3100 and RD162 are orally available drugs that bind the AR with a higher affinity, prevent AR nuclear translocation, and have no agonist activity [83]. Results from a phase 1/2 trial of MDV3100 in patients with CRPC have been encouraging, demonstrating PSA declines and bone disease responses in >50% of docetaxel-naïve patients [84]. Phase 3 trials of MDV3100 are under way in patients with metastatic CRPC. Specifically, the PREVAIL trial (NCT01212991) is accruing chemotherapy-naïve patients, while the AFFIRM trial (NCT00974311) has closed accrual of patients previously treated with docetaxel. RD162 and TOK-001 are currently undergoing phase 1/2 testing.

3.4. Treatment-related morbidity and mortality

Patients receiving hormonal therapy experience multiple toxicities as a result of testosterone and estrogen deficiency. Common side effects may affect QoL and increase overall morbidity; however, cardiovascular, metabolic, and skeletal complications are particularly concerning because of their impact on morbidity as well as mortality. Results from major studies are discussed and summarized in Table 5.

3.4.1. Cardiovascular disease—The potential association between ADT and the risk of cardiovascular disease (CVD) has been investigated in observational/retrospective studies and in secondary analyses from randomized trials.

Almost all observational/retrospective studies have been concordant in finding a correlation between long-term use of ADT and the risk of developing nonfatal CVD [3,4,6,85] or fatal CVD [3–6]. Among all endocrine treatment modalities analyzed, surgical castration [3,4] and the use of antiandrogen monotherapy [6] seemed to have a lower impact on CVD. Only in the case of a large study from a Canadian database, neither the use nor the duration of ADT was associated with an increased risk of acute myocardial infarction or sudden cardiac death [86]. Finally, short-term ADT (4 mo) may be fatal only in patients with a history of congestive heart failure or myocardial infarction [87]. In these patients, revascularization prior to the start of short-term ADT may reduce, but not eliminate, the 5-yr overall mortality risk [88].

The potential link between ADT and CVD has also been the focus of post hoc analyses from randomized trials. The combined analysis of three small RCTs of men with clinically localized PCa found that 6 mo of ADT was associated with earlier onset of fatal myocardial infarction in men aged ≤65 yr [89]. Secondary analyses of three RTOG trials (85–31, 86–10, and 92–02) showed no increased risk of cardiovascular mortality in men receiving neoadjuvant or adjuvant ADT [24,90,91]. Likewise, in the EORTC 22961 trial, 3 yr

compared with 6 mo of ADT was not associated with a higher incidence of fatal CVD (3% and 4%, respectively) [17]. Interestingly, cardiovascular mortality in EORTC 30891 was lower among patients receiving immediate ADT compared with deferred ADT (17.9% and 19.7%, respectively) [44]. Finally, in the EPC trial, cardiovascular morbidity was similar among men receiving bicalutamide 150 mg or placebo; nonetheless, deaths caused by heart failure were higher in patients in the bicalutamide arm (49 vs 25 patients) [9].

3.4.2. Insulin resistance and diabetes—Metabolic complications of ADT have been reviewed [92]. In response to ADT, patients with PCa may experience an increase in fasting insulin [93] and a decrease in insulin receptor sensitivity [94]. Four studies [3,4,86,95] have also documented an increased risk of incident diabetes secondary to ADT. This risk may be related to time of exposure [86,95].

3.4.3. Fracture risk—Several large studies have established that ADT may progressively cause a decrease in bone mineral density [96] and may increase the risk of osteoporosis and fractures [97,98]. Fracture risk was shown to be highest in long-term users of LHRH agonist and in men undergoing bilateral orchiectomy [99], while bicalutamide, when compared with leuprolide, had a lower impact on bone metabolism disorders [100]. Fractures associated with ADT may result in hospitalization and finally cause an increase in mortality [101,102].

4. Conclusions

Based on the data reviewed, indications for the use of ADT in patients with PCa are discussed. Implementation of ADT should always be evidence based, and patients should be informed about the possible adverse events and the risk–benefit ratio for ADT. Table 6 summarizes our recommendations and the corresponding levels of evidence [104].

For androgen deprivation alone compared with local standard of care, patients with clinically localized disease do not benefit from primary ADT compared with either observation or any local treatment modalities. When survival end points are considered, ADT is comparable to observation (level of evidence [LE] 1b) and inferior to RT (LE 1a) and RP (LE 3a).

For RT plus ADT compared with RT alone:

- In patients with low-risk PCa (cT1–cT2a, Gleason score 2–6, PSA <10 ng/ml), the combination of RT and ADT is comparable to RT alone (LE 1b) and thus should be discouraged.
- Patients with intermediate-risk disease (cT2b, Gleason score 7, PSA 10.1–20.0 ng/ml) may benefit from combined hormonal treatment for 4–6 mo (LE 1b).
- Patients with high-risk (cT2c or Gleason score 8–10, or PSA >20 ng/ml) and locally advanced disease are likely to benefit from combined hormonal treatment for 24–36 mo (LE 1a).
- The role of ADT in patients undergoing high-dose RT (>76 Gy) and the most appropriate extent of the radiation field require further study.

For androgen deprivation therapy given as an adjuvant after a local therapy:

- Patients with evidence of multiple lymph node metastases after surgery may benefit from early androgen deprivation (LE 1b); however, the best schedule and approach (continuous or intermittent ADT) remain undefined. The role of antiandrogen monotherapy is unknown in this case, and routine use is not indicated.

- Early ADT for men considered at high risk for development of distant metastases requires further study. Patients with high-risk local/regional disease may benefit from early treatment (LE 1b); early ADT in patients with biochemically relapsed disease (after surgery or radiation) and with short PSA doubling times (<12 mo) has shown to delay time to distant metastases, but not survival; therefore, the use of ADT in this setting cannot be routinely recommended (LE 3b). If ADT is used in these patients, a thorough understanding of the risk–benefit ratio for treatment should be necessary.

For androgen deprivation therapy in metastatic disease:

- It is widely accepted that patients with documented distant metastases should start surgical or continuous medical castration.
- For prevention of a potential disease flare, all patients starting medical castration with LHRH agonists may benefit from a short course of nonsteroidal antiandrogen 2–7 d before the start of treatment (LE 1b).
- Abiraterone acetate should be offered to patients with metastatic CRPC who progress after docetaxel chemotherapy (LE 1b).

Careful discussion of potential risks and benefits should be undertaken according to the following evidence:

- There is no definitive knowledge of the potential link between ADT and CVD. Cohort and observational studies demonstrate that ADT may affect CVD (LE 2a), while secondary analyses from RCTs do not confirm these data (LE 1b).
- ADT may induce metabolic complications; it may increase fasting insulin, decrease insulin receptor sensitivity, and finally induce incident diabetes (LE 2a).
- Long-term use of ADT may increase the risk of fracture (LE 2a) and consequently increase hospitalization and the risk of death (LE 3b).

The issues requiring further study include the role of ADT in the era of more modern/higher-dose RT for patients with microscopic lymph node metastases and patients experiencing BCR after local treatment. Similarly, the need for better definition of risk factors for complications of ADT, as well as of the role of preventive measures (changes in lifestyle and chemoprevention), requires careful prospective assessment in contemporary studies.

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Table 1

Randomized controlled trials comparing nonmetastatic patients treated with androgen deprivation therapy alone and standard of care

Data source	Population		Intervention	Follow-up, yr, median	Key findings*
	Clinical stage**	*n*			
McLeod et al. [9]	T1–T4, any N	2285	WW plus bicalutamide 150 compared with WW plus placebo	7.4	Better objective PFS with bicalutamide in locally advanced disease (0.60 [0.49–0.73]; $p < 0.001$). No OS difference in T1–T2 (1.16 [0.99–1.37]) or in locally advanced disease (0.81 [0.66–1.01]).
Widmark et al. [10]	T1–T4, N0	875	3-mo LHRH-A plus lifelong flutamide compared with same plus RT (70 Gy)	7.6	At 10 yr, the addition of RT reduced BF (0.16 [0.12–0.20]; $p < 0.0001$), CSM (0.44 [0.30–0.66]; $p < 0.0001$), and OM (0.68 [0.52–0.89]; $p = 0.004$). Urinary and sexual side effects were higher in men receiving RT.
Mottet et al. [12]	T3–T4, N0–X	263	3-yr LHRH-A compared with same plus RT (65–69 Gy)	–	5-yr PFS (60.9% vs 8.5%, $p < 0.0001$) and 5-yr metastasis-free survival (97% vs 89.2%, $p = 0.018$) in favor of the combined arm.
Warde et al. [11]	T3–T4, N0–X, or T2 and PSA >40 or T2 and PSA >20 and GS 8–10	1205	LHRH-A or orchiectomy compared with same plus RT (65–69 Gy)	6	The addition of RT reduced OM (0.77 [0.61–0.98]; $p = 0.033$). CSS was improved (0.57 [0.41–0.81]; $p = 0.001$). Late gastrointestinal toxicity rates were similar in both arms.

BF = biochemical failure; CSM = cancer-specific mortality; CSS = cancer-specific survival; GS = Gleason score; LHRH-A = luteinizing hormone–releasing hormone agonist; OM = overall mortality; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RT = radiation therapy; WW= watchful waiting.

* Unless specified differently, results are presented as hazard ratios or relative risks (treatment compared with control), with the associated 95% confidence intervals and *p* values, whenever available.

** Based on the 1992 American Joint Committee on Cancer tumor category [103].

Table 2

Randomized controlled trials comparing nonmetastatic patients treated with radiation therapy plus androgen deprivation therapy and radiation therapy alone

Data source	Population		Intervention	Follow-up, median	Key findings*
	Clinical stage**	*n*			
Jones et al. [22]	T1b–T2b, PSA ≤20	1979	4-mo LHRH-A plus RT (66.6 Gy) compared with RT alone	9.2 yr	At 10 yr, RT alone compared with ADT plus RT resulted in worse BF (41% vs 26%) (1.74 [1.48–2.04]; $p < 0.001$), CSM (8% vs 4%) (1.87 [1.27–2.74]; $p = 0.001$), and OS (57% vs 62%) (1.17 [1.01–1.35]; $p = 0.03$). In low-risk patients, RT alone compared with ADT plus RT resulted in worse BF (1.53 [1.13–2.06]; $p < 0.001$), but no difference in CSM and OS. In intermediate-risk patients, RT alone compared with ADT plus RT resulted in worse BF (1.79 [1.45–2.21]; $p < 0.001$), CSM (2.49 [1.50–4.11]; $p = 0.004$), and OS (1.23 [1.02–1.49]; $p = 0.03$). Acute and late radiation toxicity was similar in both arms.
D'Amico et al. [29]	T1b–T2b, intermediate/ high risk, N0	206	6-mo LHRH-A plus RT (70 Gy) compared with RT alone	7.6 yr	RT alone compared with RT plus ADT resulted in worse OM (44 vs 30 deaths) (1.8 [1.1–2.9], $p = 0.01$) and CSM (14 vs 4 deaths) (4.1 [1.4–12.1]; $p = 0.01$).
Crook et al. [19]	T1c–T4, N0; of the total, 26% were low risk, 43% intermediate risk, and 31% high risk	378	ST (3 mo) compared with LT (8 mo) LHRH-A plus flutamide plus RT (70 Gy)	44 mo	No outcome difference between the two arms.
Pilepich et al. [23]	T3–T4, any N	945	LHRH-A given indefinitely plus RT (65–70 Gy) compared with RT alone	7.6 yr	At 10 yr, ADT plus RT compared with RT alone resulted in better OS (49% vs 39%, $p = 0.002$), LF (23% vs 38%, $p < 0.0001$), DM (24% vs 39%, $p < 0.001$), and CSM (16% vs 22%, $p = 0.0052$).
Roach et al. [24]	T2–T4, any N	456	4-mo LHRH-A plus RT (65–70 Gy) compared with RT alone	11.9 yr	At 10 yr, ADT plus RT compared with RT alone resulted in better CSM (23% vs 36%, $p = 0.01$), DM (35% vs 47%, $p = 0.006$), DFS (11% vs 3%, $p = 0.0001$), and BF (65% vs 80%; $p < 0.0001$). No significant difference in OS.
Bolla et al. [18]	T2–T4, any N	401	36-mo LHRH-A plus RT (70 Gy) compared with RT alone	9.1 yr	At 10 yr, RT alone compared with ADT plus RT resulted in worse DFS (22.7% vs 47.7%) (0.42 [0.33–0.55]; $p < 0.0001$), OS (39.8% vs 58.1%) (0.60 [0.45–0.80]; $p = 0.0004$), and CSM (30.4% vs 10.3%) (0.38 [0.24–0.60]; $p < 0.0001$).
Denham et al. [20]	T2b–T4, N0	537	6-mo LHRH-A plus RT (66 Gy) compared with RT alone	5.9 yr	ADT plus RT compared with RT alone resulted in better LF (0.42 [0.28–0.62]; $p < 0.0001$), BF (0.58 [0.46–0.74]; $p < 0.0001$), DFS (0.56 [0.45–0.69]; $p < 0.0001$), DM (0.67 [0.45–0.99]; $p = 0.046$), and CSS (0.56 [0.32–0.98]; $p = 0.04$).

Data source	Population		Intervention	Follow-up, median	Key findings*
	Clinical stage**	*n*			
Granfors et al. [21]	T2–T4, any N	91	Orchiectomy plus RT (65 Gy) compared with RT alone	14–19 yr	RT alone compared with RT plus ADT resulted in worse OM (87% vs 76%, p= 0.03), and CSM (57% vs 36%, p = 0.02).
See et al. [25]	T1–T4, any N	1368	Bicalutamide 150 mg given indefinitely plus RT (64 Gy) compared with RT alone	7.2 yr	In locally advanced disease, bicalutamide plus RT compared with placebo plus RT resulted in better PFS (0.56 [0.40–0.78]; p < 0.001), BF (0.41 [0.30–0.55]; p < 0.001), and OS (0.65 [0.44–0.95]; p = 0.03). No difference in localized disease.
Horwitz et al. [32]	T2–T4, any N	1554	ST (4 mo) compared with LT (24 mo) LHRH-A plus RT (70 Gy)	11.3 yr	At 10 yr, ST compared with LT treatment resulted in worse DFS (13.2% vs 22.5%, p < 0.0001), CSS (83.9% vs 88.7%, p = 0.0042), LF (22.2% vs 12.3%, p < 0.0001), DM (22.8% vs 14.8%, p < 0.0001), and BF (68.1% vs 51.9%, p < 0.0001). Only among men with GS 8–10, OS was improved by LT treatment (31.9% vs 45.1%, p = 0.0061).
Bolla et al. [17]	T1c–T2a–b pN+ or T2–T4 any N	970	ST (6 mo) compared with LT (36 mo) LHRH-A plus RT (70 Gy)	6.4 yr	At 5 yr, ST compared with LT treatment resulted in worse CSM (4.7% vs 3.2%) (1.71 [1.14–2.57], p = 0.002) and OM (19% vs 15.2%) (1.42 [1.09–1.85], p = 0.65 for noninferiority).

ADT = androgen deprivation therapy; BF = biochemical failure; CSM = cancer-specific mortality; CSS = cancer-specific survival; DFS = disease-free survival; DM = distant metastases; GS = Gleason score; LF = local failure; LHRH-A = luteinizing hormone–releasing hormone agonist; LT = long-term; OM = overall mortality; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RT = radiation therapy; ST = short-term.

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**Based on the 1992 American Joint Committee on Cancer tumor category [103].

Table 3

Randomized controlled trials in nonmetastatic patients receiving adjuvant androgen deprivation therapy

Data source	Population		Intervention	Follow-up, yr, median	Key finding*
	Clinical stage**	*n*			
Messing et al. [39,40]	pT2–pT4, pN+	98	RP plus immediate castration (LHRH-A or orchiectomy) compared with RP plus castration at clinical progression	11.9	Immediate castration improved PFS (3.42 [1.96–5.98]; $p < 0.0001$), CSS (4.09 [1.76–9.49]; $p = 0.0004$), and OS (1.84 [1.01–3.35]; $p = 0.04$]. Baseline PSA was not available.
McLeod et al. [42]	pT2–pT4, any N	4454	RP plus bicalutamide 150 mg compared with RP plus placebo	7.4	PFS difference was improved only in men with locally advanced disease (0.75 [0.61–0.91]; $p = 0.004$). OS was comparable (1.09 [0.85–1.39], $p = 0.51$).
Studer et al. [44]	Any cT, any N	985	Immediate castration (LHRH-A or orchiectomy) compared with castration at clinical progression	7.8	Slightly better OS for immediate treatment (1.25 [1.05–1.48]; $p > 0.1$ for noninferiority). No significant difference in CSS or symptom-free survival.
Schröder et al. [43]	Any cT, N+	234	Immediate castration (LHRH-A or orchiectomy) compared with castration at clinical or PSA progression	13	No significant difference in OS (1.22 [0.92–1.62]). However, the trial is underpowered to show noninferiority of deferred castration.

CSS = cancer-specific survival; LHRH-A = luteinizing hormone–releasing hormone agonist; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; RP = radical prostatectomy.

* Unless specified differently, results are presented as hazard ratios or relative risks (treatment compared with control), with the associated 95% confidence intervals and *p* values, whenever available.

** Based on the 1992 American Joint Committee on Cancer tumor category [103].

Table 4

Selected randomized controlled trials of androgen deprivation therapy in patients with metastatic prostate cancer

Data source	Population		Intervention	Follow-up, yr, median	Key findings*
	Clinical stage**	*n*			
Crawford et al. [57]	100% M+	603	CAB (leuprolide + flutamide) compared with leuprolide plus placebo	–	The addition of flutamide resulted in longer PFS (16.5 vs 13.9 mo, $p = 0.039$), OS (35.6 vs 28.3 mo, $p = 0.035$), and reduced disease flare expressed as pain at first week ($p = 0.019$) and fourth week ($p = 0.013$).
Eisenberger et al. [59]	100% M+	1387	CAB (orchiectomy plus flutamide) compared with orchiectomy plus placebo	–	PSA response was improved in men receiving flutamide ($p < 0.001$); OS was not significantly different ($p = 0.14$).
Dijkman et al. [58]	100% M+	457	CAB (orchiectomy plus nilutamide) compared with orchiectomy plus placebo	8.5	At 8.5 yr, CAB resulted in better PFS (21.2 vs 14.7 mo, $p = 0.002$), CSS (37.0 vs 29.8 mo, $p = 0.013$), and OS (27.3 vs 23.6 mo, $p = 0.033$).
Boccardo et al. [56]	35% M0 and 65% M+	373	CAB (goserelin plus flutamide) compared with goserelin plus placebo	2	At 2 yr, CAB vs monotherapy resulted in no PFS or OS difference.
Tyrrel [71]	T3–T4, M0 and M+	589	Bicalutamide 150 mg compared with monotherapy***	2	At 2 yr, in M+ men bicalutamide compared with monotherapy resulted in worse OS (HR: 1.30 for time to death); data immature for evaluation of M0 men.
PCTCG [60]	Meta-analysis of 27 RCTs; population composed of 12% M0 and 88% M+	8275	CAB (orchiectomy or LHRH-A plus flutamide, nilutamide, or CPA) compared with monotherapy***	5	At 2 or 5 yr, CAB compared with monotherapy resulted in no OS difference. However, CAB with nilutamide or flutamide resulted in better OS (27.6% vs 24.7%, $p = 0.005$), while CAB with CPA resulted in worse OS (15.4% vs 18.1%, $p = 0.04$).
Collette et al. [61]	Reanalysis of PCTCG excluding trials without disease flare protection; population composition not specified	4764	Orchiectomy compared with CAB (11 trials) or monotherapy*** plus ST-AA compared with CAB (4 trials)	–	Exclusion of trials without disease flare protection from PCTCG meta-analysis results in no survival benefit of maximal androgen blockade over monotherapy (0.95 [0.89–1.02]; $p = 0.15$).

CAB = combined androgen blockade; CPA = cyproterone acetate; CSS = cancer-specific survival; HR = hazard ratio; LHRH-A = luteinizing hormone–releasing hormone agonist; OS = overall survival; PCTCG = Prostate Cancer Trialists' Collaborative Group; PFS = progression-free survival; PSA = prostate-specific antigen; RCT = randomized controlled trial; ST-AA = short-term antiandrogens.

* Unless specified differently, results are presented as hazard ratios or relative risks (treatment compared with control), with the associated 95% confidence intervals and *p* values, whenever available.

** Based on the 1992 American Joint Committee on Cancer tumor category [103].

*** Monotherapy: orchiectomy or LHRH-A.

Table 5

Treatment-related morbidity and mortality

Data source	Population	Follow-up, median	Key findings*
Cardiovascular			
Keating et al. [3]	73 196 men aged ≥66 yr with locoregional PCa; 36.3% received LHRH-A and 6.9% underwent orchiectomy.	4.5 yr	Use of LHRH-A, but not orchiectomy, resulted in higher risk of CHD (1.16 [1.10–1.21]; $p < 0.001$), MI (1.11 [1.01–1.2]; $p = 0.03$), and sudden cardiac death (1.16 [1.05–1.27]; $p = 0.004$).
Keating et al. [4]	37 443 men with median age 66.9 yr and locoregional PCa; 39% received some form of ADT.	2.6 yr	Use of LHRH-A resulted in higher risk of CHD (1.19 [1.10–1.28]), MI (1.28 [1.08–1.52]), sudden cardiac death (1.35 [1.18–1.54]), and stroke (1.22 [1.10–1.36]). Orchiectomy resulted in higher risk of CHD (1.40 [1.04–1.87]) and MI (2.11 [1.27–3.50]).
Saigal et al. [85]	22 816 men aged ≥66 yr with any stage PCa; 21% received LHRH-A; analysis controlled for age, race, comorbidity score, history of heart disease, and other factors.	>5 yr	Use of LHRH-A resulted in higher overall cardiovascular morbidity (1.20 [1.15–1.26]; $p < 0.05$).
Tsai et al. [5]	4892 men with localized PCa received a local treatment; of the total, 1015 also received medical ADT.	3.8 yr	Use of ADT resulted in higher risk of cardiovascular mortality in the RP group (2.6 [1.4–4.7]; $p = 0.002$) but not in the RT, cryotherapy, or brachytherapy group (1.2 [0.8–1.9]; $p = 0.40$).
Alibhai et al. [86]	Men aged ≥66 yr; 19 079 men receiving ADT matched with 19 079 controls; ADT was medical or surgical.	6.5 yr	Use of ADT did not result in higher risk of MI (0.92 [0.84–1.00]; $p > 0.05$) or cardiac mortality (0.96 [0.83–1.10]; $p > 0.05$).
Van Hemelrijck et al. [6]	76 600 men with PCa; the 30 642 men who underwent medical or surgical ADT were compared with men undergoing curative treatment or surveillance.	3.5 yr	Risk of cardiovascular morbidity was elevated in all men, being the highest for those undergoing ADT. SIR: 1.40 (1.31–1.49), 1.15 (1.01–1.31), and 1.20 (1.11–1.30) for men undergoing ADT, curative treatment, and surveillance, respectively.
Nanda et al. [87]	5077 with cT1–cT3 N0M0 PCa, median age 69.5 yr; 1521 of these patients received 4 mo of neoadjuvant ADT.	>4.5 yr	Neoadjuvant ADT resulted in higher risk of all-cause mortality only among men with history of MI or heart failure (1.96 [1.04–3.71]; $p = 0.04$).
D'Amico et al. [89]	1372 men of all ages with localized PCa enrolled in one of three trials comparing RT with or without ADT.	>4.8 yr	Time to fatal MI was shorter in men receiving 6 mo of ADT plus RT compared with RT alone ($p = 0.017$); effect seen only in men aged ≥65 yr.
Efstathiou et al. [90]	945 men of all ages with locally advanced PCa randomized to RT plus immediate or deferrd ADT; data derived from trial RTOG 8531.	8.1 yr	Longer use of ADT did not result in higher cardiovascular mortality (0.73 [0.47–1.15]; $p = 0.16$).
Roach et al. [24]	456 men of all ages with locally advanced PCa treated with RT plus ADT (4 mo) vs RT alone; data derived from trial RTOG 8610.	11.9 yr	At 10 yr, RT plus ADT compared with RT did not result in higher cardiovascular mortality (12.5% vs 9.1%, $p = 0.32$).
Efstathiou et al. [91]	1554 men with locally advanced PCa randomized to RT plus 4 mo of ADT or RT plus 28 mo of ADT;	11.3 yr	Longer use of ADT did not result in higher cardiovascular

Data source	Population	Follow-up, median	Key findings*
	data derived from trial RTOG 9202.		mortality (1.09 [0.81–1.47]; $p = 0.58$).
Bolla et al. [17]	1113 men with locally advanced PCa randomized to RT plus 6 mo ADT or RT plus 3 yr ADT; data derived from trial EORTC 22961.	6.4 yr	At 5 yr, longer use of ADT did not result in higher cardiovascular mortality: 4.0% in short-term arm and 3.0% in long-term arm (p not provided).
Studer et al. [44]	985 men of all ages with locally advanced or N+ PCa randomized to immediate vs delayed ADT; data derived from trial EORTC 30891.	7.8 yr	Men receiving immediate compared with deferred ADT had lower cardiovascular mortality (17.9% and 19.7%; p not provided).
McLeod et al. [9]	8053 men with localized and locally advanced PCa randomized to standard of care plus bicalutamide or placebo; data derived from EPC trial.	7.4 yr	Men receiving bicalutamide compared with placebo were at higher risk for heart failure (1.2% and 0.6%) but not for MI (2% and 1.9%) or stroke (1.2% and 1.1%).
Diabetes			
Keating et al. [3]	73 196 men aged ≥66 yr with locoregional PCa; 36.3% received LHRH-A and 6.9% underwent orchiectomy.	4.5 yr	Both use of LHRH-A and orchiectomy resulted in higher risk of incident diabetes (1.44 [1.34–1.55]; $p < 0.001$ and 1.34 [1.20–1.50]; $p < 0.001$), respectively.
Keating et al. [4]	37 443 men with median age 66.9 yr and locoregional Pca; 39% received some form of ADT.	2.6 yr	Use of LHRH-A resulted in higher risk of incident diabetes (1.28 [1.19–1.38]).
Alibhai et al. [86]	Men aged ≥66 yr with Pca; 19 079 men receiving ADT matched with 19 079 controls.	6.5 yr	Use of ADT resulted in higher risk of incident diabetes (1.24 [1.15–1.35]; $p < 0.05$).
Lage et al. [95]	1231 men with PCa who received ADT compared with 7250 men with PCa who did not receive ADT.	–	Use of ADT resulted in higher risk of incident diabetes both at 12 mo (1.36 [1.07–1.74]; $p = 0.01$) and 18 mo (1.49 [1.12–1.99]).
Fracture risk			
Shahinian et al. [99]	50 613 men with Pca, of whom 31.1% received LHRH-A or underwent orchiectomy.	≥12 mo	Dose-dependent increase in the risk of fractures. Orchiectomy and LHRH-A (≥9 doses) resulted in the highest increase in the risk for any fracture and fractures requiring hospitalization.
Smith et al. [97]	3887 men aged ≥65 yr with any stage PCa who received LHRH-A were compared with 7774 nontreated men with same PCa.	7 yr	Use of ADT resulted in increased risk of any fracture (1.25 [1.09–1.45]; $p < 0.0001$), vertebral fracture (1.25 [1.09–1.45]; $p < 0.0001$), and hip–femur fracture (1.36 [1.14–1.62]; $p = 0.0006$).
Abrahamsen et al. [98]	15 716 men diagnosed with fractures and 47 149 matched controls controlled for PCa diagnosis and ADT.	–	Use of ADT resulted in increased risk of any fracture (1.7 [1.2–2.5]; $p < 0.0001$) and of hip fracture (1.9 [1.2–3.0]; $p < 0.05$) but not of vertebral fracture.
Alibhai [86]	Men aged ≥66 yr with PCa; 19 079 men receiving ADT matched with 19 079 controls.	6.5 yr	Use of ADT resulted in higher risk of fragility fracture (1.65 [1.53–1.77]; $p < 0.0001$).

ADT = androgen deprivation therapy; CHD = coronary heart disease; EORTC = European Organisation for Research and Treatment of Cancer; EPC = Early Prostate Cancer; LHRH-A = luteinizing hormone–releasing hormone agonist; MI = myocardial infarction; PCa = prostate cancer; RP = radical prostatectomy; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; SIR = standardized incidence ratios.

*Unless specified differently, results are presented as hazard ratios or relative risks (treatment compared with control), with the associated 95% confidence intervals and p values, whenever available.

** Level of evidence is defined according to the Oxford Centre for Evidence-Based Medicine [104].

Table 6

Summary of recommendations for the use of androgen deprivation therapy in patients with prostate cancer

Clinical setting	Is androgen deprivation therapy recommended?	LE*	Ref
ADT alone compared with local standard of care			
Compared with observation	No	1b	[7–9]
Compared with radiotherapy	No	1a	[10,11]
Compared with surgery	No	3a	[13–16]
RT plus ADT compared with RT alone			
Low risk	No	1b	[22,27,28]
Intermediate risk	Yes: 4–6 mo of ADT should be combined to RT	1b	[22,29]
High risk	Yes: 24–36 mo of ADT should be combined to RT	1a	[17,18,20,21, 23,25,30,32]
ADT adjuvant after a local therapy			
N+	Yes: patients with multiple LN metastases should receive LHRH-A	1b	[39,40]
Local–regional disease	Consider ADT only in patients at high risk for developing distant metastases (GS ≥8, PSA DT <12 mo)	1b	[44]
PSA failure	Consider ADT only in patients at high risk for developing distant metastases (GS ≥8, PSA DT <12 mo)	3b	[46,47]
ADT in metastatic disease			
Start at diagnosis	Yes: surgical or chemical castration with continous LHRH-A	–	
Disease flare prevention with AA	Yes in all patients, 2–7 d before LHRH-A start	1b	[57,63]
Abiraterone acetate	Yes in docetaxel-treated patients with CRPC	1b	[81]

AA = antiandrogens; ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; GS = Gleason score; LHRH-A = luteinizing hormone – releasing hormone agonist; LE = level of evidence; LN = lymph node; PSA = prostate-specific antigen; PSA DT = prostate-specific antigen doubling time; Ref = reference; RT = radiation therapy.

* LE is defined according to the Oxford Centre for Evidence-Based Medicine [104].