Androgen deprivation therapy for prostate cancer—review of indications in 2010

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ABSTRACT

The discovery of androgen deprivation therapy (ADT) has been one of the most important advances in the treatment of prostate cancer. Here, the indications for the use of ADT are reviewed, together with the data supporting each indication. The settings for ADT use include cytoreduction; combined ADT and radiotherapy; pathologic node-positive disease; and recurrent, metastatic, or progressive prostate cancer.

KEY WORDS

Androgen antagonists, hormonal anti-neoplastic agents, combined-modality therapy, disease progression, orchiectomy, prostatic neoplasms, radiotherapy, prostatectomy

1. INTRODUCTION

Prostate cancer (PCa) is the most common noncutaneous malignancy in men. Many patients will do well with single-modality treatment, including radical prostatectomy, external-beam radiotherapy (RT), and brachytherapy. However, for locally advanced disease, multimodality therapy—including androgen derivation therapy (ADT)—is required to improve outcomes.

Different types of ADT can be used. Luteinizing-hormone releasing-hormone agonists (LHRHas) are the agents most commonly used. Although orchiectomy is a cost-effective method of long-term androgen deprivation, it is rarely used [1]. The LHRH antagonist degarelix has shown equivalency to LHRHa in a large randomized study [2] and has received a Health Canada "no objection" letter. Combined androgen blockade (CAB) is the combination of a LHRHa and an anti-androgen. In the present review, "use of ADT" refers to the use of a LHRHa with or without a nonsteroidal anti-androgen (NSAA). Patient risk groups are classified per D'Amico *et al.* [3].

Here, we review the current indications for ADT in the treatment of PCa (Table I). The role of ADT in cytoreduction is discussed first. The evidence for combined ADT and RT in the radical and postoperative settings and for ADT in pathologically lymph-node positive patients is then reviewed. Finally, the use of ADT to treat locally recurrent, progressive, and metastatic PCa is discussed.

2. DISCUSSION

2.1 Cytoreduction

Brachytherapy, either alone or in combination with RT, is a standard treatment option for men with low-risk PCa. The use of brachytherapy is related to prostate size. The American Brachytherapy Society has suggested that a prostate larger than 60 mL is a relative contraindication to interstitial brachytherapy because of the technical difficulties related to interference from the pubic arch bone and to the increased number of seeds [4], although the more important criteria clinically is the shape of the axial prostate in relation to the ischial tuberosity arch when the patient is in the treatment position. Androgen deprivation therapy for 3–6 months can be used to cytoreduce the prostate to allow for an adequate implant.

After 3 months of LHRHa with or without a NSAA, prostate volume decreases by between 23% and 48% [5–7]. Although most shrinkage occurs in the first 3 months, continued ADT can result in additional cytoreduction until 9 months [8]. The Crook *et al.* article on 3 months versus 8 months of neoadjuvant ADT showed that, compared with duration of ADT, differences between patients were a greater predictor of prostate-specific androgen (PSA) response [9]. That hypothesis remains untested, but a corollary that may reasonably follow is that some patients may cytoreduce faster than others, and a reasonable approach may be to monitor PSA closely and to redo the arch study when the patient's PSA first reaches undetectable levels. This way, some men may be spared a longer course of ADT than is necessary. Another, less common option is the combination of a 5α-reductase inhibitor (5ARI) and NSAA to avoid the side effects of LHRHa. In one study, that combination reduced prostate volume by 34% [10].

TABLE I Summary of treatment recommendations

Clinical setting	*Recommendation*
Cytoreduction	Luteinizing-hormone releasing hormone agonist (LHRHa) or combined androgen blockade (CAB) for 3–6 months.
Intermediate-risk disease	Uncertain benefit for short-term androgen derivation therapy (ADT) when dose-escalated (>70 Gy) radiotherapy (RT) is being delivered, but ADT can be considered. If lower doses (<70 Gy) of RT are being used, then short-term ADT should be added.
High-risk disease	Combined RT and long-term ADT. The use of ADT without RT should be avoided.
Postoperative patient	Combined adjuvant or salvage RT with long-term ADT can be considered.
Lymph-node-positive disease	Optimal treatment remains controversial, with conflicting randomized evidence.
Metastatic, recurrent, or progressive disease	Any of LHRHa or orchiectomy, nonsteroidal anti-androgen monotherapy, or CAB can be considered. Timing of ADT for asymptomatic patients is unclear, and prognostic factors including doubling time for prostate-specific antigen (PSA), PSA response to ADT, Gleason score, and age can be used in decision-making.

For low-risk patients who do not tolerate LHRHa or NSAA, an alternative is to use a 5ARI alone. However, the selected agent must be administered longer, and the cytoreduction is less than that achieved with LHRHa. In a randomized controlled trial (RCT) of patients with benign prostatic hypertrophy, finasteride for 1 year reduced prostate volume by 17% [11]. However, given the lack of anti-neoplastic activity with a 5ARI as compared with a LHRHa, patients should be monitored on an active surveillance protocol [12] until definitively treated.

Neoadjuvant ADT can also be used for cytoreduction before external-beam RT to improve the geometry of the prostate in relation to adjacent organs at risk and to lower the dose to rectum, bladder, and small bowel [13,14]. However, with the advanced RT techniques currently available, the theoretical benefit of such a strategy is diminished, and the question remains untested to date.

2.2 ADT and RT

Given the excellent results with single-modality treatment for low-risk PCa, ADT has no role in the primary treatment of low-risk patients outside of the cytoreduction already discussed. For intermediate-risk patients, there is some evidence to support the short-duration use of ADT. Finally, in high-risk patients, a number of RCTs support long-term ADT combined with RT.

2.2.1 Intermediate-Risk Patients

To date, most trials examining the use of ADT and RT have focused on high-risk patients. As a result, the evidence supporting ADT in the treatment of intermediate-risk PCa is more limited, and where benefit was shown, the doses of RT were low by contemporaneous standards (total effective dose: <70 Gy delivered in 2-Gy daily fractions).

A study from Harvard randomized 206 patients with T1b–T2b disease and PSA 10–40 ng/mL or a Gleason score of 7 or higher to 70 Gy RT alone or in combination with 6 months of ADT starting 2 months before RT [15]. After 4.5 years' median follow-up, the addition of ADT was associated with statistically significant improvements in overall survival [OS (5-year: 88% vs. 78%; $p = 0.04$)], cancer-specific survival (CSS), and survival free of salvage ADT. Most patients in the trial were at intermediate risk, but a small proportion of patients were at high risk (15% had Gleason scores of 8–10; 12% had PSA levels of more than 20 ng/mL).

The results from the Radiation Therapy Oncology Group (RTOG) trial 94-08 were recently presented in abstract form [16]. That trial randomized patients with T1b–T2b disease and a PSA level of 20 ng/mL or less to 66.6 Gy alone or with 4 months of ADT starting 2 months before RT. Pelvic lymph nodes received 46.8 Gy. The 2028 patients enrolled had a median follow-up of 8.3 years. Short-term ADT improved OS at 12 years to 51% (RT+ADT) from 46% (RT alone; $p = 0.03$).

In a Canadian study by Crook *et al.* [9], 378 men were randomized to either 3 months or 8 months of CAB before 66 Gy external-beam RT. Intermediate-risk patients accounted for 43% of the study population. No differences were observed in the failure rates (biochemical, local, or distant) for the overall population, but in subgroup analyses, a nonsignificant trend to improved disease-free survival (DFS) favouring longer ADT was noted in high-risk patients.

The Trans-Tasman Radiation Oncology Group (TROG) conducted a 3-arm study that randomized patients with locally advanced PCa to 66 Gy RT alone, to RT with 3 months of ADT, or to RT with 6 months of ADT [17]. Distinct from the Canadian study, the TROG trial had a much lower proportion of intermediate-risk patients (16%) and many more high-risk patients (84%). Compared with no ADT, ADT for 6 months resulted in improved 5-year local, distant, biochemical failure-free, and PCa–specific survival; DFS;

and freedom from salvage treatment. Longer ADT (6 months vs. 3 months) resulted in improved distant failure and freedom from salvage treatment, and also a trend toward better PCa–specific survival.

The foregoing studies suggest an overall and cancer-specific survival benefit for short-term ADT when combined with conventional-dose RT (66–70 Gy) for the treatment of intermediate-risk disease. However, it is unclear if that benefit persists in the current era of dose-escalated (>70 Gy) RT, which has been shown to improve biochemical DFS in multiple randomized studies without ADT [18–20].

2.2.2 High-Risk Patients

Multiple RCTs have established a role for combined ADT and RT in the treatment of high-risk PCa. The RTOG 8531 trial compared RT combined with either immediate (adjuvant) ADT or delayed ADT at progression [21] in patients with clinical T3 or N1 disease. The RT consisted of pelvic RT with a boost to the prostate to 65–70 Gy. At 10 years, adjuvant ADT improved OS (49% vs. 39%, $p = 0.002$), which was preferentially seen in patients with Gleason scores of 7–10. Adjuvant ADT also improved cancer-specific mortality, local failure, and distant metastases. The RTOG 8610 trial treated patients having bulky T2–T4 disease with RT or RT and 4 months of neoadjuvant and concurrent ADT [22]. The RT dose, fractionation, and volume were the same as in RTOG 8531. Addition of ADT was associated with statistically significant improvements in cause-specific mortality, biochemical DFS, distant metastases, and local control. No OS benefit was seen in the overall population; but in subgroup analyses, an OS benefit was found for Gleason 2–6 tumours. Taking those trials together, it would appear that high-grade disease benefits from long-term ADT and that bulky lower-grade disease may benefit from short-term ADT.

The European Organisation for Research and Treatment of Cancer (EORTC) also conducted a study comparing RT alone with RT and 3 years of ADT in patients with T1–T2 World Health Organization grade 3 or T3–T4 N0–N1 M0 tumours. After a median of 66 months of follow-up, 5-year OS was 62% in the RT-alone arm and 78% in the combined-treatment arm ($p = 0.0002$) [23].

The optimal duration of ADT was investigated in two trials. In RTOG 9202, patients were randomized to 4 or 28 months of ADT, both beginning 2 months before RT [24]. Patients had T2c–T4 disease and PSA below 150 ng/mL; they underwent pelvic RT with a prostate boost to 65–70 Gy. Long-term ADT significantly improved all outcomes (CSS, DFS, biochemical failure, distant metastases, local control) except OS. However, subgroup analyses found that patients with Gleason scores of 8–10 experienced an OS benefit with 28 months ADT (5-year OS: 81% vs. 71%; $p = 0.044$).

The EORTC also conducted a non-inferiority study for patients with either T1c–T2b and pathologic N1–N2, or T2c–T4 and clinical N0–N2 disease [25]. Patients were randomized to 6 or 36 months of ADT, beginning on the first day of RT. Pelvic RT with a prostate boost to 70 Gy was used. Compared with short-term ADT, long-term administration resulted in a lower 5-year overall mortality (15.2% vs. 19.0%, $p = 0.65$ for non-inferiority) and also lower prostate-specific mortality (3.2% vs. 4.7%, $p = 0.0002$).

The RTOG 9413 trial addressed the optimal timing of ADT relative to RT [26]. This 4-arm trial compared whole-pelvis with prostate-only RT and neoadjuvant–concurrent with adjuvant ADT. For all groups, the ADT duration was 4 months. Patients were required to have an estimated risk of lymph node involvement of more than 15% [27]. If given, whole-pelvis RT reached 50.4 Gy, and the prostate received 70.2 Gy. The authors observed no significant difference in progression-free survival (PFS) between neoadjuvant and adjuvant ADT. However, the interactions between RT field size and timing of ADT are complex. In subset analyses of patients receiving whole-pelvis RT, there was an unexpected finding: as compared with patients receiving adjuvant ADT, those receiving neoadjuvant ADT experienced improved OS ($p = 0.019$) and PFS ($p = 0.022$). The same result was not found for patients receiving prostate-only RT. Also, because the trial used only 4 months of ADT, it is unclear whether long-term ADT for high-risk patients would show the same interaction.

2.2.3 ADT Alone for High-Risk Patients

The importance of RT in the management of locally advanced high-risk PCa was demonstrated in a randomized trial reported by Widmark *et al.* [28] that compared ADT alone with combined ADT and RT. The ADT consisted of 3 months of CAB, followed by continuous flutamide until progression or death. After a median of 7.6 years' follow-up, the addition of RT to ADT resulted in an improved 10-year overall mortality of 29.6% compared with 39.4% in the ADT-alone group ($p = 0.004$). The 10-year cancer-specific mortality was also lower in the combined RT and ADT arm: 11.9% versus 23.9% ($p < 0.001$). Side effects with the addition of RT were acceptable compared with those seen with ADT alone. Based on this study, patients with locally advanced PCa should receive combined RT and ADT, and the use of ADT alone should be avoided.

2.2.4 Postoperative Patients

Currently, no published RCT has compared RT alone with RT and ADT in the postoperative setting. However, combined therapy is important, given the publication of two RCTs demonstrating improved biochemical DFS [29,30] and OS [29] with adjuvant RT (as compared with observation) after radical prostatectomy in patients with pathologic T3 or margin-positive disease.

In the salvage setting for patients with rising PSA after radical prostatectomy, two trials are of interest. The RTOG 9601 trial comparing salvage RT with or

without 2 years of bicalutamide 150 mg for patients with PSA relapse after radical prostatectomy has been completed, and results are pending. The currently open RTOG 0534 trial is a 3-arm trial comparing salvage RT alone with 4–6 months of ADT and with ADT plus pelvic nodal RT. In addition, the U.K. Medical Research Council and National Cancer Institute of Canada RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery) trial continues to accrue patients in whom postoperative RT is indicated. Participants are randomized to early or delayed RT and also to 0, 6, or 24 months of ADT with LHRHa.

Phase II data in the adjuvant (undetectable PSA) and salvage (rising PSA) settings have shown that the combination of postoperative RT and 2 years of ADT is well tolerated, with encouraging rates of DFS and OS [31,32]. For patients with rising PSA, salvage RT to 60–66 Gy and ADT resulted in a 7-year freedom from PSA relapse rate of 78.6% and an OS of 93.2% [31]. Although those results compare favourably with the results from a multi-institutional postoperative salvage RT series with a 6-year bDFS of 32% [33], the patients in the former cohort were censored at biochemical failure, and thus the rates of castrate-resistant disease or of OS after initiation of ADT are unknown. For patients with undetectable postoperative PSA, but with pathologic T3 or margin-positive disease, RT to 60–66 Gy and ADT resulted in a 7-year PSA relapse–free rate of 97.6% and an OS of 93.1% [32].

2.3 Pathologic Lymph-Node-Positive PCa

Two trials that looked at the benefit of early ADT in patients with pathologic lymph-node-positive PCa have produced conflicting results. The Eastern Cooperative Oncology Group (ECOG) found that, as compared with deferred treatment, immediate ADT improved OS, CSS, and PFS [34]. After a median follow-up of 11.9 years, overall mortality rates were 36%and 55% in the early and deferred ADT arms respectively [hazard ratio (HR): 1.84; $p = 0.04$]. Prostate cancer–specific deaths were also lower in the early ADT group: 15% versus 49% (HR: 4.09; $p = 0.0004$).

In contrast, the EORTC also conducted a study comparing early and deferred ADT in pathologic node-positive disease [35]. The main difference from the ECOG study was that radical prostatectomy was not completed. After a median follow-up of 8.7 years, no difference in OS was observed [HR: 1.23; 95% confidence interval (CI): 0.88 to 1.71]. Prostate cancer–specific death rates were not statistically significantly different in the two arms (46.2% for early ADT vs. 47.0% for deferred ADT, p value not reported).

It has been hypothesized that the difference in results between the two trials is attributable to the completion of radical prostatectomy in the ECOG trial [35]. That hypothesis would need to be confirmed in a RCT. However, such a trial will be unlikely given the poor accrual and premature closure of both studies and the rarity of pathologic lymph node positive disease in this era of PSA screening.

2.4 Metastatic, Recurrent, or Progressive PCa

A systematic literature review and guidelines from the American Society of Clinical Oncology regarding the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive PCa (Loblaw *et al.* [36]) has been published. Readers are referred to that publication for a detailed analysis.

The standard initial treatment options for these patients consist of either bilateral orchiectomy or LHRHa. Monotherapy with NSAA may be considered as an alternative, but a systematic review of the literature and meta-analysis [37] found a trend toward worse OS with NSAA than with orchiectomy (HR: 1.2158; 95% CI: 0.988 to 1.496). Steroidal anti-androgen monotherapy should not be offered because, in a RCT in which it was compared with goserelin [38], it resulted in a worse time to progression.

The evidence concerning the additional benefit of CAB as compared with castration alone is conflicting. Three meta-analyses [39–41] have indicated that CAB may modestly improve survival. In the largest systematic review, which included a meta-analysis of individual patient data, the Prostate Cancer Trialists Collaborative Group (PCTCG) found that CAB using NSAA (flutamide or nilutamide) reduced mortality to 72.4% from 75.3% with castration alone ($p < 0.005$) [41]. That evidence for benefit is balanced by a systematic review that found that, compared with castration alone, CAB was associated with increased risk of diarrhea (10% vs. 2%), gastrointestinal pain (7% vs. 2%), and nonspecific ophthalmologic events (29% vs. 5%) [40]. An update from a RCT comparing CAB plus bicalutamide with LHRHa alone found that, after a median of 5.2 year of follow-up, CAB was associated with improved OS (HR: 0.78; 95% CI: 0.60 to 0.99; $p = 0.0498$) [42]. However, there was no difference in CSS between the groups. It should be noted that studies using bicalutamide were not included in the PCTCG meta-analysis because none had been published at that time. Bicalutamide also has a better toxicity profile than the alternative NSAA [43,44], and it has little additional toxicity compared with LHRHa alone [45]. Given the potential survival benefit with NSAA and the lower toxicity profile of bicalutamide, patients should be advised about CAB using this agent and counselled accordingly.

Early-versus-deferred ADT continues to be investigated. For patients who are symptomatic from PCa, ADT should be initiated. However, for asymptomatic patients, the timing ADT initiation is unclear. In asymptomatic patients who have a rising PSA as the only manifestation of disease after radical treatment (radiation or surgery) and who also have non-castrate levels of testosterone, no published

RCT is available to guide therapy. The ELAAT (Early versus Late Androgen Ablation Therapy) trial by the Ontario Clinical Oncology Group and the TOAD (Timing of Androgen Deprivation) trial by the TROG are both currently enrolling patients and are designed to answer that question.

Five RCTs have been published [46–50] relating to patients who have not undergone radical treatment to the prostate, who have non-castrate levels of testosterone, and who have metastases detectable on imaging (patients with pathologically involved lymph nodes are also considered to be in this detectable metastases group—see the discussion at "Pathologic Lymph-Node-Positive PCa," earlier). Results from those trials are conflicting. Combining the randomized data for the asymptomatic clinical states being addressed, early ADT was found to be associated with a modest reduction (17%) in relative risk for PCa–specific mortality, a moderate increase (15%) in relative risk for non-PCa-specific mortality, and no OS advantage [36] compared with deferred ADT at the time of symptom onset. In the authors' practice, ADT is initiated based on prognostic factors including PSA doubling time, PSA response to ADT, Gleason score, and age.

3. SUMMARY

The discovery of ADT has been one of the most important advances in the treatment of PCa. Although significant progress has been made in optimizing ADT use, many questions remain, and clinical trials should be considered, if available. Paramount to ADT use is a detailed discussion of the potential harms of treatment, which are covered in a separate section of this supplement. Only through a careful consideration of the benefits and risks of ADT will the best outcomes be realized for PCa patients.

4. REFERENCES

1. Loblaw DA, Pickles T, Cheung PC, Lukka H, Faria S, Klotz L. Hormone use after radiotherapy failure: a survey of Canadian uro-oncology specialists. *Can Urol Assoc J* 2009;3:460–4.
2. Klotz L, Boccon–Gibod L, Shore ND, *et al*. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int* 2008;102:1531–8.
3. D'Amico AV, Whittington R, Malkowicz SB, *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969–74.
4. Nag S, Beyer D, Friedland J, Grimm P, Nath R. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 1999;44:789–99.
5. Whittington R, Broderick GA, Arger P, *et al*. The effect of androgen deprivation on the early changes in prostate volume following transperineal ultrasound guided interstitial therapy for localized carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1999;44:1107–10.
6. Pinault S, Tetu B, Gagnon J, Monfette G, Dupont A, Labrie F. Transrectal ultrasound evaluation of local prostate cancer in patients treated with LHRH agonist and in combination with flutamide. *Urology* 1992;39:254–61.
7. Gleave ME, Goldenberg SL, Chin JL, *et al*. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. *J Urol* 2001;166:500–6.
8. Lilleby W, Fossa SD, Knutsen BH, Abildgaard A, Skovlund E, Lien HH. Computed tomography/magnetic resonance based volume changes of the primary tumour in patients with prostate cancer with or without androgen deprivation. *Radiother Oncol* 2000;57:195–200.
9. Crook J, Ludgate C, Malone S, *et al*. Report of a multicenter Canadian phase III randomized trial of 3 months vs. 8 months neoadjuvant androgen deprivation before standard-dose radiotherapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;60:15–23.
10. Merrick GS, Butler WM, Wallner KE, Galbreath RW, Allen ZA, Kurko B. Efficacy of neoadjuvant bicalutamide and dutasteride as a cytoreductive regimen before prostate brachytherapy. *Urology* 2006;68:116–20.
11. Lepor H, Williford WO, Barry MJ, *et al*. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *N Engl J Med* 1996;335:533–9.
12. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol* 2010;28:126–31.
13. Zelefsky MJ, Leibel SA, Burman CM, *et al*. Neoadjuvant hormonal therapy improves the therapeutic ratio in patients with bulky prostatic cancer treated with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 1994;29:755–61.
14. Forman JD, Kumar R, Haas G, Montie J, Porter AT, Mesina CF. Neoadjuvant hormonal downsizing of localized carcinoma of the prostate: effects on the volume of normal tissue irradiation. *Cancer Invest* 1995;13:8–15.
15. D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-Month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004;292:821–7.
16. McGowan DG, Hunt D, Jones CU, *et al*. Short-term endocrine therapy prior to and during radiation therapy improves overall survival in patients with T1b–T2b adenocarcinoma of the prostate and PSA # 20: initial results of RTOG 94-08. *Int J Radiat Oncol Biol Phys* 2010;77:1–4.
17. Denham JW, Steigler A, Lamb DS, *et al*. Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. *Lancet Oncol* 2005;6:841–50.
18. Zietman AL, Bae K, Slater JD, *et al*. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term

results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol* 2010;28:1106–11.
19. Al-Mamgani A, van Putten WL, Heemsbergen WD, *et al*. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72:980–8.
20. Kuban DA, Tucker SL, Dong L, *et al*. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67–74.
21. Pilepich MV, Winter K, Lawton CA, *et al*. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005;61:1285–90.
22. Pilepich MV, Winter K, John MJ, *et al*. Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;50:1243–52.
23. Bolla M, Collette L, Blank L, *et al*. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002;360:103–6.
24. Horwitz EM, Bae K, Hanks GE, *et al*. Ten-year follow-up of Radiation Therapy Oncology Group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. *J Clin Oncol* 2008;26:2497–504.
25. Bolla M, de Reijke TM, Van Tienhoven G, *et al*. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;360:2516–27.
26. Lawton CA, DeSilvio M, Roach M 3rd, *et al*. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys* 2007;69:646–55.
27. Roach M 3rd, Marquez C, Yuo HS, *et al*. Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1994;28:33–7.
28. Widmark A, Klepp O, Solberg A, *et al*. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009;373:301–8.
29. Thompson IM, Tangen CM, Paradelo J, *et al*. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009;181:956–62.
30. Bolla M, van Poppel H, Collette L, *et al*. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005;366:572–8.
31. Choo R, Danjoux C, Gardner S, *et al*. Efficacy of salvage radiotherapy plus 2-year androgen suppression for postradical prostatectomy patients with PSA relapse. *Int J Radiat Oncol Biol Phys* 2009;75:983–9.
32. Choo R, Danjoux C, Gardner S, *et al.* Prospective study evaluating postoperative radiotherapy plus 2-year androgen suppression for post-radical prostatectomy patients with pathologic T3 disease and/or positive surgical margins. *Int J Radiat Oncol Biol Phys* 2009;75:407–12.
33. Stephenson AJ, Scardino PT, Kattan MW, *et al*. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007;25:2035–41.
34. Messing EM, Manola J, Yao J, *et al*. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006;7:472–9.
35. Schroder FH, Kurth KH, Fossa SD, *et al*. Early versus delayed endocrine treatment of pN1–3 M0 prostate cancer without local treatment of the primary tumor: results of European Organisation for the Research and Treatment of Cancer 30846—a phase III study. *J Urol* 2004;172:923–7.
36. Loblaw DA, Virgo KS, Nam R, *et al*. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2007;25:1596–605.
37. Seidenfeld J, Samson DJ, Hasselblad V, *et al*. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med* 2000;132:566–77.
38. Thorpe SC, Azmatullah S, Fellows GJ, Gingell JC, O'Boyle PJ. A prospective, randomised study to compare goserelin acetate (Zoladex) versus cyproterone acetate (Cyprostat) versus a combination of the two in the treatment of metastatic prostatic carcinoma. *Eur Urol* 1996;29:47–54.
39. Samson DJ, Seidenfeld J, Schmitt B, *et al*. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer* 2002;95:361–76.
40. Schmitt B, Wilt TJ, Schellhammer PF, *et al*. Combined androgen blockade with nonsteroidal antiandrogens for advanced prostate cancer: a systematic review. *Urology* 2001;57:727–32.
41. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000;355:1491–8.
42. Akaza H, Hinotsu S, Usami M, *et al*. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. *Cancer* 2009;115:3437–45.
43. McLeod DG. Tolerability of nonsteroidal antiandrogens in the treatment of advanced prostate cancer. *Oncologist* 1997;2:18–27.
44. Schellhammer PF, Sharifi R, Block NL, *et al*. Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized, multicenter trial. Casodex Combination Study Group. *Urology* 1997;50:330–6.
45. Akaza H, Yamaguchi A, Matsuda T, *et al*. Superior antitumour efficacy of bicalutamide 80 mg in combination with a luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist monotherapy as first-line treatment for advanced prostate cancer: interim results of a randomized study in Japanese patients. *Jpn J Clin Oncol* 2004;34:20–8.

46. McLeod DG, Iversen P, See WA, *et al*. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006;97:247–54.
47. Studer UE, Hauri D, Hanselmann S, *et al*. Immediate versus deferred hormonal treatment for patients with prostate cancer who are not suitable for curative local treatment: results of the randomized trial SAKK 08/88. *J Clin Oncol* 2004;22:4109–18.
48. Studer UE, Whelan P, Albrecht W, *et al*. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) trial 30891. *J Clin Oncol* 2006;24:1868–76.
49. Kirk D. Timing and choice of androgen ablation. *Prostate Cancer Prostatic Dis* 2004;7:217–22.
50. Byar DP. Proceedings: the Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate. *Cancer* 1973;32:1126–30.

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