Combining radiation therapy and androgen deprivation for localized prostate cancer—a critical review

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ABSTRACT

Interest has been increasing in the use of androgen deprivation therapy (ADT) combined with radiation therapy (RT) in the management of localized prostate cancer. Preclinical studies have provided some rationale for the use of this combination. In patients with high-risk disease, the benefit of a combined approach, with the addition of adjuvant hormonal therapy, is supported by results of randomized trials. In contrast, for patients with low-risk disease, there is no obvious therapeutic advantage except for cytoreduction. The usefulness of short-term hormonal therapy in association with RT for intermediate-risk patients is still debatable, particularly in the context of dose-escalated RT. The optimal timing and duration of ADT, in the neoadjuvant and adjuvant settings alike, are still under investigation. In view of the potential side effects with ADT, further studies are being performed to better identify subsets of patients who will definitely benefit from this therapy in combination with RT.

KEY WORDS

Prostate cancer, radiotherapy, hormonal therapy, androgen deprivation therapy, combined treatment

1. INTRODUCTION

Although the worldwide incidence rates of prostate cancer (PCa) vary greatly, in Western countries, where screening programs are more developed, PCa remains one of the most frequent cancers and a leading cause of cancer death [1]. The current main treatment modalities for localized PCa are radical prostatectomy, radiation therapy (RT) with or without androgen deprivation therapy (ADT), and active surveillance.

For nearly a century, RT alone has been used in the curative treatment of localized PCa [2]; however, approximately one third of patients with localized disease will present with treatment failure within 5 years of treatment [3,4]. These failures are probably related not only to known predictive factors such as prostate-specific antigen (PSA), Gleason score (GS), and T stage, but also to factors associated with intrinsic tumour radioresistance or micrometastatic disease at diagnosis (or both) [5–7]. Possible alternatives to improve RT results include higher doses of irradiation and agents that optimize the radiation effect.

After a study published by Huggins and Hodges [8] in 1941 demonstrated the androgen dependence of prostatic cells, the use of hormonal therapy (HT) was widely explored in the management of PCa, and since the mid-1970s, pharmacologic castration has been used as an alternative to surgical castration. Reversibility to a normally functioning hypothalamic–pituitary–testicular axis and the absence of possible psychological effects related to orchiectomy have popularized the use of pharmacologic therapy. In the early years, estrogen in the form of diethylstilbestrol (DES) was used successfully for androgen suppression [9]. However, the use of DES has been almost abandoned in the management of PCa because of its significant thromboembolic and cardiovascular toxicity [10,11]. Currently, various classes of drugs are available in the market, including luteinizing hormone–releasing hormone (LHRH) agonists (the most commonly used agents), LHRH antagonists, and anti-androgens.

For metastatic disease, the usefulness of ADT is supported by randomized trials, and it is the mainstay of treatment [12,13]. In an attempt to improve results for localized PCa, the use of ADT with RT has been studied for several decades [14]. In the present article, we critically review the results of randomized trials of RT combined with ADT for the treatment of localized PCa.

2. MATERIALS AND METHODS

Data for the present study were identified by a structured MEDLINE search to November 1, 2009. The search combined the terms "prostate cancer," "hormones," "androgen deprivation," "randomized trial," "phase 3," and "radiotherapy." Only publications in English were considered. All randomized trials comparing the combined use of a LHRH agonist and external-beam RT for nonmetastatic localized

PCa (experimental arm) with RT alone (standard arm) were included and reviewed. Trials using hormonal therapy with brachytherapy, either alone or in combination with external-beam RT, were excluded. Trials that included surgical castration or estrogen therapy as options for hormonal suppression were similarly excluded. Abstracts from meetings were considered for the analysis.

Twelve randomized studies potentially suitable for this review were identified in total, but only nine (grouped as neoadjuvant or adjuvant trials) were considered directly relevant for a more detailed critical analysis. Articles were excluded when they were preliminary reports on acceptability of treatment [15] and when they used bicalutamide or DES as the ADT method [14,16,17].

For the purpose of this review, we adopted the definition of risk stratification set out by the Genito-Urinary Radiation Oncologists of Canada [18]:

- Low risk: ≤ T2a, PSA ≤ 10 ng/dL, and GS < 7
- Intermediate risk: T2b–T2c, or PSA 10–20 ng/dL, or GS = 7
- High risk: ≥T3a, or PSA > 20 ng/dL, or GS > 7

3. RESULTS

3.1 Biological Basis for Combined Treatment

The benefits anticipated from the combination of ADT and RT are based on several experimental studies. Zietman *et al.* [19,20] showed that androgen deprivation reduces the dose of RT necessary to control 50% of the tumour (TCD_{50}). Nude mice bearing Shionogi adenocarcinoma allograft were treated with radiation with or without orchiectomy at varying times. It was observed that the combination of RT and ADT provided better tumour control and that the timing of ADT plays an important role in this combined therapy. Orchiectomy 12 days before (neoadjuvant) radiation produced a significantly greater decline in the TCD_{50} than if performed during or after RT.

Kaminski *et al.* [21] not only reported increased overall tumour-cell kill in animal models, but also a longer doubling time in the surviving PCa cells after neoadjuvant treatment. Rats bearing Dunning rat PCa cell lines were treated with RT and temporary ADT (orchiectomy followed by testosterone replacement) at varying times. As compared with RT given during or before the 14 days of ADT, temporary ADT for 14 days before RT resulted in a statistically significant lengthening of tumour growth. This study hypothesized a protracted effect on tumour growth after neoadjuvant ADT even after androgen levels are restored.

The effect of hypoxia on PCa has been extensively studied in recent years. Low oxygen levels in PCa tumours are known to be associated with treatment failure and poor prognosis [22]. Prostate tumours often have an erratic and inefficient pattern of vascularization, which leads to intermittent or chronic hypoxia [23]. Inadequate tissue oxygenation is the prime trigger of angiogenesis, in which several angiogenic factors, including vascular endothelial growth factor and its receptors, are expressed [24]. Androgen deprivation has been shown to downregulate expression of vascular endothelial growth factor, causing apoptosis of endothelial cells and consequently decreased vascularization. Thus, ADT may have a role in at least a transient "normalization" of tumour vascularization not only by reducing leaky immature tumour vessels, but also by causing the death of perivascular cells and thus causing decreased interstitial pressure [25–27]. Measurements of vascular efficiency such as microvascular density [28,29] and vascular morphology [30] have been shown to be promising predictors of clinical outcome. Doppler ultrasound has demonstrated decreased vascular resistance as result of ADT use [31,32]. Milosevic *et al.* [33] studied 237 PCa patients and reported significant heterogeneity in prostate oxygenation, with median pO_2 ranging from 0 mmHg to 75 mmHg. In addition, they were the first authors to prove clinically that ADT increases PCa oxygenation [34]. Thus, although understanding is far from complete, the effects of ADT on tissue vascularization and hypoxia seem to make important contributions to the additive effect seen with combined treatment.

Systemically, ADT may prevent the dissemination of micrometastasis because of inhibition of DNA synthesis and cell proliferation, and an increased apoptotic ratio [35]. There is also some evidence of a tumoricidal immune system response triggered by androgen suppression [36]. Despite many preclinical trials providing a theoretical basis for ADT prescription, several mechanisms still lack further elucidation.

3.2 Low-Risk Disease

Overall, low-risk patients are characterized by excellent long-term outcomes regardless of treatment option. According to the CAPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) database, the number of patients with favourable low-risk disease receiving ADT as primary or neoadjuvant treatment since the start of the PSA era is growing, despite a lack of prospective randomized data [37].

No randomized trial has yet compared ADT plus RT with RT alone in patients with low-risk disease. The Radiation Therapy Oncology Group (RTOG) protocol 94-08 was a randomized trial that assessed whether a combination of total androgen blockade for 2 months before and 2 months during definitive RT, as compared with RT alone, would improve overall survival (OS) in patients with T1b–T2b disease, PSA below 20 ng/dL, and no involved nodes [38]. Although not designed specifically for low-risk disease, a subgroup analysis that included 685 patients in the low-risk stratification (GS 6 or less, with PSA 10 ng/dL or lower, and less than

T2b) showed no statistically significant difference between combined therapy and RT alone for OS (76% vs. 73%) or disease-specific survival [DSS (98% vs. 99%)] at 8 years. There was, however, a significant decline in the biochemical failure rate favouring the combined treatment arm [20% vs. 30%; hazard ratio (HR): 1.53; 95% confidence interval (CI): 1.13 to 2.06]. These results are to be viewed with caution and only as hypothesis-generating, because the trial was not designed or powered for this stratification group and also because the dose of RT delivered (66.6 Gy in 37 fractions) is considered below the current recommended standard.

Until results from randomized trials specifically designed for this group of patients are available, whether a clinical benefit results from combined treatment will remain unknown. Currently, RT alone should be considered the treatment of choice.

3.3 Intermediate-Risk and High-Risk Disease

Most trials clustered intermediate-risk and high-risk patients together and did not treat them based on risk stratification. For the purposes of the present paper, we treated these groups as one and analyzed the results based on whether patients received hormonal therapy in the neoadjuvant or adjuvant setting.

3.3.1 Neoadjuvant Trials

Five randomized trials have directly compared the use of ADT before and during RT with RT alone (Table I). Not only were these trial conducted in different eras, they also differed in several other aspects, including patient selection, scheduling and duration of hormonal therapy, RT delivery, and definition of endpoints.

Patient Selection and ADT Schedule: RTOG 86-10 [39,40] was the first trial to test the hypothesis that short-term neoadjuvant ADT combined with RT can improve treatment outcomes in patients with locally advanced disease. From 1987 to 1991, 456 patients with bulky T2–T4 disease (≥5×5 cm of palpable tumour) were randomized to receive either RT alone or ADT with goserelin and flutamide for 2 months before and 2 months concomitantly with RT. Patients with involved pelvic nodes were also eligible. This trial was initiated before the PSA era, and PSA measurements were available for only 29% of the patients. The median PSA for those patients was 26.3 ng/dL, which denotes the high-risk population of the study. Additionally, after central pathology review, 66% of the patients were considered to have a Gleason score of 7 or more.

The Quebec L-101 study [41] randomly allocated 161 patients with clinical stage T2–T3 tumours to RT alone; to 3 months of neoadjuvant treatment before RT; or to ADT 3 months before, 2 months during, and 5 months after RT. Among those patients, 70% had T2 tumours, and 74.5% had a GS of 6 or lower. Median PSA ranged from 9 ng/dL to 12 ng/dL, thus conferring to most of these patients characteristics considerably less aggressive than are typically seen in other neoadjuvant studies.

D'Amico *et al.* [42,43] compared 6 months of total ADT (2 months before, during, and after RT) with RT alone. The study enrolled 206 patients with clinical stage T1b–2b N0 M0 and at least 1 unfavourable prognostic factor. Unfavourable prognostic factors were a PSA above 10 ng/dL (maximum: 40 ng/dL), GS 7–10, and evidence (by endorectal magnetic resonance imaging) of extracapsular extension or seminal vesicle invasion. In this trial, 79% of the patients were classified as intermediate-risk; the remaining 21% were high-risk.

The Trans-Tasman Radiation Oncology Group (TROG) 9601 study [44] accrued 818 men with stage T2b–T4 without evidence of lymph node metastasis. No limit for PSA was initially set for eligibility. Patients were randomized to RT alone; 3 months of total ADT and RT, with neoadjuvant ADT starting 2 months before RT; or 6 months of total ADT with neoadjuvant ADT starting 5 months before RT. Basically, this study included a larger proportion of high-risk patients (83%) who had a PSA of 20 ng/dL or more (38%), T3–4 disease (40%), or GS 8 or higher (17%).

The RTOG 94-08 protocol [38] described earlier studied whether a short course of ADT (same scheme used in RTOG 86-10) improves OS in localized PCa (T1b–T2b, PSA ≤ 20 ng/dL, and no involved nodes). Most of the patients accrued were intermediate-risk (54%), with low-risk patients being the next largest group (35%); a small number were high-risk patients (11%).

Radiation Therapy Schemes: In these trials, the RT varied significantly in terms of clinical target volume and dose delivered. In RTOG studies 86-10 and 94-08 [38,40], RT was typically delivered electively to the whole pelvis to a dose of 44–46 Gy, with the prostatic target volume boosted to a total dose of 65–70 Gy. Patients in the Quebec L-101 study [41] received 64 Gy of RT, using field sizes of 8×8 cm to 10×10 cm. For those in the TROG 9601 [44] and D'Amico *et al.* [43] studies, pelvic lymph nodes were clearly not included in the clinical target volume. In the TROG 9601 study, RT was delivered to the prostate and seminal vesicles to a total dose of 66 Gy. In the D'Amico *et al.* trial, 45 Gy was given to the prostate and seminal vesicles, followed by 22 Gy to the prostate volume only.

Outcomes: Table I summarizes the outcomes of the randomized neoadjuvant trials. Two studies showed a significantly statistical OS benefit for combined treatment. In the D'Amico *et al.* trial [43], a statistically significantly improved 8-year OS [74% (95% CI: 64%–82%) vs. 61% (95% CI: 49%–71%)] was seen for men receiving RT with ADT as compared with those receiving RT alone ($p = 0.01$). That study population was composed mostly of intermediate-risk patients, with about 20% of the patients harbouring

TABLE I Completed phase III trials studying neoadjuvant androgen deprivation therapy

Reference	*Pts (n)*	*Risk group*	*RT (Gy)*	*Hormonal therapy (HT)*	*Median follow-up (years)*	*Scheme (HT months)*	*Timing of HT*			*Local failure*	*Biochemical NED*	*Overall survival*
							Pre-RT (months)	*RT (months)*	*Post-RT (months)*			
Pilepich *et al.*, 2001 [39],	456	High	65–70	TAB	13.2	RT alone					20	34
Roach *et al.*, 2008 [40] (RTOG 86-10)		(bulky disease)			11.9	RT + HT (4)	2	2		(10 years, p=0.18[a])	35 (10 years, p=0.0001)	42 (10 years, p=0.12)
Laverdiere *et al.*, 2004 [41]	161	Intermediate	64	TAB	5	RT alone				NR	42	NR
(Quebec L-101)		(~70%)				RT + HT (3)	3				66	
						RT + HT (10)	3	2	5		69 (7 years, p<0.05[b])	
D'Amico *et al.*, 2004 [42],	206	Intermediate	70	TAB	7.6	RT alone				NR	55	61
D'Amico *et al.*, 2008 [43]		(79%)				RT + HT (6)	2	2	2		79 (5 years, p<0.05)	74 (8 years, p=0.01)
Denham *et al.*, 2005 [44]	802	High	66	TAB	5.9	RT alone				28	38	NR
(TROG 96-01)		(84%) Intermediate (16%)				RT + HT (3)	2	5		17	52	
						RT + HT (6)	2	2		12 (5 years, p<0.05[b])	56 (5 years, p<0.05[b])	
McGowan *et al.*, 2009 [38]	1979	Low	66	TAB	9.2	RT alone				39	59	57
(RTOG 94-08)		(35%) Intermediate (54%) High (11%)			9.1	RT + HT (4)	2	2		21 (2 years[c], p=0.001)	74 (10 years, p=0.01)	62 (10 years, p=0.03)

[a] No failure rates given.
[b] No statistically significant difference between the hormonal therapy arms.
[c] Positive re-biopsies at 2 years.
Pts = patients; RT = radiation therapy; NED = no evidence of disease; TAB = total androgen blockade; NR = not reported.

high-risk factors. In a post-randomization analysis of the study, the authors evaluated the benefit of ADT by risk group [45]. That subgroup analysis suggested that the addition of 6 months of ADT is associated with improved survival in intermediate-risk ($p = 0.01$) and high-risk ($p = 0.06$) disease alike, although the absolute magnitude of the survival difference seems to benefit mostly the group of patients with intermediate-risk disease. That benefit appears to depend on the patient's level of comorbidities, however. Regardless of risk group stratification, post-randomization assessment of the interaction between level of comorbidity and all-cause mortality has shown that patients with moderate or severe comorbidities did not experience similar survival benefits when ADT was added to RT [43]. In the D'Amico *et al.* trial, deaths from causes other than PCa were inexplicably higher in number in the RT-alone arm. It is also important to note that the cancer-specific death rate in the RT-alone arm at 5 years (14 deaths vs. 4 deaths for combined treatment at the same time point; HR: 4.1; 95% CI: 1.4 to 12.1; $p = 0.01$) is considered higher than that usually observed for the same group of patients treated by RT alone.

Recently, the results of RTOG 94-08 [38] (presented in abstract form) also showed an OS benefit for the use of a short course of neoadjuvant hormonal therapy. In that trial, 10-year OS improved to 62% from 57% (HR: 1.17; 95% CI: 1.01 to 1.35; $p = 0.03$). Analysis by risk category demonstrated that 54% of the patients fit into the intermediate-risk category (GS 7 or GS ≤ 6, and either PSA 10–20 ng/dL or T2b). Those patients showed the largest benefit for all endpoints at 8 years, with a statistically significant improvement in OS to 72% from 66% and in DSS to 98% from 92%. The OS and DSS HRs were 1.23 and 2.44 respectively—both larger than for the study population as a whole. On subset analysis of high-risk patients, no statistically significant improvement in OS and DSS was found with the addition of 4 months of HT. The small number of patients in the high-risk group (only 11% of the total) and the short duration of the HT may explain the lack of benefit. Although this trial accrued a large number of patients and has a long follow-up, with PSA levels available for all patients, a direct extrapolation of these results to daily practice is still premature considering the hypothesis-generating nature of the subgroup analysis. Additionally, the RT dose used (66.6 Gy in 37 fractions) is certainly below the current standard.

The RTOG 86-10 trial provided data on 10-year OS and showed no significant improvement for combined treatment over control [40]. At a median follow-up of 11.9 years, the authors reported a 10-year OS of 42.6% for combined treatment and 33.8% for RT alone ($p = 0.12$). A subgroup analysis showed that patients having a GS of 6 or lower benefited significantly as compared with those having a GS of 7 or higher (5-year OS: 70% vs. 52%; $p = 0.015$) [39]. However, this positive outcome was based on a central histopathology review and not on the original institutional GS used for the randomization. Deaths resulting from PCa at 8 and 10 years were significantly lower with the short course of HT: 23% as compared with 33% ($p = 0.05$) and 23% as compared with 36% ($p = 0.01$) respectively. It is important to keep in mind that this trial preceded the PSA era, accepted patients with positive nodes, and required a minimum tumour size of 5×5 cm in eligible patients.

In terms of biochemical failure rates, all five neoadjuvant studies showed statistically significant improvements over RT alone for patients receiving combined treatment (Table I). However, varying follow-up durations and varying criteria for biochemical failure post-RT have been used, making direct comparison between series very difficult, if not inappropriate. The only trials using the recently adopted "PSA nadir + 2 ng/mL" Phoenix criteria [46] were the TROG 9601 and RTOG 94-08 protocols.

Local disease control at 5 years was significantly improved in the TROG 9601 study. In the RT-alone group, local failures occurred at a rate of 28% as compared with 17% and 12% in the 3-month and 6-month HT groups respectively (HR: 0.42; 95% CI: 0.28 to 0.62; $p = 0.0001$). In that trial, 6 months of HT was not statistically superior to 3 months (HR: 0.75; 95% CI: 0.49 to 1.16; $p = 0.196$]. In the RTOG 86-10 trial, the difference in local progression was not statistically significant at 10 years ($p = 0.18$); however, specific rates in each risk group were not reported. In RTOG 94-08, 2-year re-biopsies were performed in 843 of 1979 accrued patients. Of those biopsies, 21% in the combined-treatment group were positive as compared with 39% in the RT-alone group ($p < 0.01$).

The RTOG 86-10 trial showed significant improvement in the distant metastasis rate. Men who received ADT plus RT had an estimated 10-year distant metastasis rate of 34.9% (95% CI: 28.5% to 41.3%) as compared with 46.9% in those who received RT alone (95% CI: 40.3% to 53.5%). These data have suggested a possible role for ADT in postponing systemic progression. In the TROG 9601 study, 3 months of HT plus RT was not sufficient to reduce the risk of distant metastasis; however, 6 months of treatment was statistically superior both to 3 months of ADT plus RT and to RT alone, suggesting that 3 months of HT may not be sufficient for a systemic benefit. It must be kept in mind that the positive effect observed in these studies with the longer HT duration may be related to long-term or even permanent castration [47,48].

In summary, the use of neoadjuvant HT in combination with RT has consistently shown improvements in biochemical failure rates, and two trials unequivocally showed an overall survival benefit. The trials included a heterogeneous group of patients with intermediate-risk and high-risk disease, different endpoints, and different treatments, making an objective interpretation of the results rather difficult. Further studies with a proper definition of risk stratification are clearly needed in this area.

Duration of Neoadjuvant Therapy: The optimal duration of HT and the timing of RT in men who undergo neoadjuvant ADT are uncertain. In most studies, RT begins 2–3 months after ADT begins. In a multicentre Canadian trial [49,50], 378 men with low-risk (n = 98), intermediate-risk (n = 163), or high-risk (n = 117) localized disease were randomized to conventional-dose RT (66 Gy) with either 3 months or 8 months of neoadjuvant ADT. At a median follow-up of 6.6 years, disease-free survival, OS, and patterns of failure were similar in both groups. However, 8 months of neoadjuvant ADT was associated with a significant prolongation of 7-year disease-free survival for men with high-risk disease (59% vs. 33%, p = 0.01). An update of the Canadian study [51] showed that the biochemical response to neoadjuvant ADT before RT, and not duration of HT, appears to be the most critical determinant of benefit in the setting of combined therapy. Men achieving a PSA of 0.1 ng/dL or less before RT seem to achieve significantly higher biochemical control than do those whose pre-RT PSA is above 0.1 ng/dL (55.3% vs. 49.4%, p = 0.014). If this provocative finding proves to be real, the neoadjuvant HT duration may be individually tailored to the PSA nadir, avoiding unnecessary hormone-related toxicities and costs. The RTOG 99-10 trial, a similar study for intermediate-risk patients only, completed accrual of more than 1500 patients in 2004. Results of that trial are forthcoming.

3.3.2 Adjuvant Trials

Four randomized trials compared adjuvant HT post-RT to no further treatment [41,52–57]. Table II provides details about those studies. One trial using bicalutamide as the HT [17] is not included in the present analysis. As with the studies in the neoadjuvant setting, trials of adjuvant HT vary in several aspects.

Patient Selection and ADT Schedule: In the European Organisation for Research and Treatment of Cancer (EORTC) 22863 study, 415 patients with T1–2 World Health Organization histopathologic grade 3 (9%) or T3–4 (any histopathologic grade) N0–1 (91%) disease were randomized to RT alone or to RT with concurrent and adjuvant ADT. Patients received HT on the first day of RT and continued on it for 36 months. Cyproterone, an anti-androgen, was given for 1 month before ADT. The RTOG 92-02 trial randomized 1554 patients to 24 months of ADT or to no further treatment after 2 months of neoadjuvant HT and 2 months of HT given concomitantly with RT. Patients with T2c–T4 N0–Nx disease and a PSA below 150 ng/dL were included. The RTOG 85-31 trial randomized 945 patients with clinical stage T3 (57%), postoperative extracapsular or seminal vesicle involvement (15%), or nodal disease (28%) to RT alone or to RT with adjuvant ADT starting in the last week of RT and given indefinitely or until evidence of disease progression. Finally, the Quebec L-200 study compared neoadjuvant and concomitant ADT (total of 5 months) with neoadjuvant, concomitant, and short-course adjuvant ADT (total of 10 months). Among the 296 eligible patients with T2–T3 disease, 30% were T3, 30% had a GS of 7 or higher, and median PSA level was 9.4 ng/dL.

Radiation Therapy Schemes: These trials were not greatly different in terms of RT dose prescription. In RTOG 85-31, RTOG 92-02, and EORTC 22863, pelvic irradiation for all patients was planned to a total dose of 44–46 Gy, followed by a boost of 20–25 Gy to the prostate, thus achieving a total dose of 70 Gy. A lower total dose of 64 Gy was delivered in the Quebec L-200 study, using field sizes of 8×8 cm to 10×10 cm.

Outcomes: Mortality from all causes was significantly lower in two trials, EORTC 22863 and RTOG 85-31 (Table II). The former trial was the first to show a survival benefit with combined treatment for locally advanced PCa. At a median follow-up of 66 months, in patients receiving ADT for 36 months, the 5-year survival rate was 78% compared with 62% in the RT-only group (p = 0·0002; HR: 0·51; 95% CI: 0·36 to 0·73). The long-term results of the RTOG 85-31 study [53] confirmed the significant improvement in DSS and absolute survival for patients receiving combined treatment. Notably, although ADT was supposed to be taken for life, its median duration was only 2.2 years [58].

Compared with neoadjuvant and concurrent HT, 24 months of HT after neoadjuvant and concurrent HT, per RTOG 92-02, has not significantly improved 10-year OS except in patients with a GS of 8 or higher. The lack of survival benefit in the RTOG 92-02 study may be a result of the large number of patients with a GS of 7 or higher (70%) or of the shorter duration of HT compared with that in the EORTC 22863 trial.

Except for the Quebec L-200 trial, the other studies (EORTC 22863, RTOG 92-02, RTOG 85-31) have all shown statistically significant improvements in biochemical control. However, biochemical failure was defined using different criteria in those studies, making a comparison of outcomes not reliable.

The RTOG 85-31, EORTC 22863, and RTOG 9202 studies all showed a significant reduction in local and distant failure rates with the use of HT and RT. The significant benefit in local control supports the additive and perhaps supra-additive effects observed in experimental models [20,21,59].

Duration of Adjuvant Therapy: A recent study, EORTC 22961 [60], used a non-inferiority design to compare RT plus 36 months of ADT with the same RT plus 6 months of ADT. It enrolled good-performance patients (970 evaluable) with stage T1c–T2b, pathologic nodal stage N1–N2, and no clinical evidence of metastatic spread (M0), or with clinical tumour stages T2c–T4, clinical nodal stages N0–N2, and no clinical evidence of metastatic spread. After receiving RT plus 6 months

TABLE II Completed phase III trials studying adjuvant androgen deprivation therapy

Reference	*Pts* (n)	*Risk group*	*RT (Gy)*	*Hormonal therapy (HT)*	*Median follow-up (years)*	*Scheme (HT months)*	*Timing of HT*			*Local failure*	*Biochemical NED*	*Distant metastasis*	*Overall survival*
							Pre-RT (months)	*RT (months)*	*Post-RT (months)*				
Pilepich *et al.*, 1997 [52]	945	High	65–70	PAB	7.6	RT alone		(final week)	(indefinite)	38	9	39	39
Pilepich *et al.*, 2005 [53] (RTOG 8531)						RT+ HT (indefinite)				23 (10 years, $p<0.05$)	31 (10 years, $p=0.0001$)	24 (10 years, $p=0.0001$)	49 (10 years, $p=0.002$)
Bolla *et al.*, 1997 [54]	412	High	70	PAB	5.5	RT alone				7	45	29	62
Bolla *et al.*, 2002 [55] (EORTC 22863)						RT + HT (36)		2	34	1 (5 years, $p<0.05$)	76 (5 years, $p<0.05$)	10 (5 years, $p<0.05$)	78 (5 years, $p=0.00002$)
Hanks *et al.*, 2003 [56]	1554	High	70	PAB	5.8	RT + HT (4)	2	2		22	32	23	51
Horwitz *et al.*, 2008 [57] (RTOG 9202)						RT + HT (24)	2	2	24	12 (10 years, $p<0.05$)	48 (10 years, $p<0.05$)	15 (10 years, $p<0.05$)	54 (10 years, $p=0.36$)
Laverdiere *et al.*, 2004 [41]	296	Low	66	TAB	3.7	RT + HT (5)	3	2		NR	70	NR	NR
(Quebec L-200)		(25%) Intermediate (41%) High (34%)				RT + HT (10)	3	2	5		70 (4 years, $p=0.55$)		

Pts = patients; RT = radiation therapy; NED = no evidence of disease; PAB = partial androgen blockade; TAB = total androgen blockade; NR = not reported.

of ADT, these patients were randomized to no further HT (short-term arm) or to another 30 months of HT (long-term arm). After a median follow-up of 6.4 years, the 5-year overall mortality was 19.0% and 15.2% (HR: 1.42; upper 95.71% confidence limit: 1.79; $p = 0.65$ for non-inferiority) for short-term and long-term suppression respectively, and the prostate-specific mortality was 4.7% and 3.2% respectively (HR: 1.71; 95% CI: 1.14 to 2.57; $p = 0.002$ by the log-rank test). Despite of the relatively short follow-up period, this report confirms the importance of long-term HT for high-risk patients.

A provocative hypothesis-generating secondary analysis of the RTOG 85-31 study [58] reported that, as compared with a shorter duration, prolonged HT with LHRH agonist for more than 5 years might be associated with improved outcomes in patients with locally advanced localized PCa. In a nonrandomized fashion, D'Amico *et al.* [61] compared short-term versus long-term HT from a pooled analysis of patients enrolled in three prospective randomized trials and treated either with 36 or 6 months of androgen suppression and pelvic RT. They concluded that the longer use of hormonal therapy was not associated with increased survival.

Quebec PCS IV (principal investigator: Dr. A. Nabid) is a recently completed study that randomized more than 600 patients with high-risk disease to 18 or 36 months of HT, both arms receiving RT. The forthcoming results of that Quebec trial, together with those of the ongoing RADAR study [62] that is comparing 6 months with 18 months of HT, will hopefully shed further light on this intriguing and important scheduling question.

3.3.3 ADT in the Dose Escalation Context

Level 1 evidence [63–68] indicates that, compared with conventional RT doses (<74 Gy), RT dose escalation provides better biochemical control rates. Trials comparing RT alone with RT plus HT used RT doses that are now considered suboptimal local therapy, particularly in terms of PSA control. Whether dose escalation beyond the doses used in most of the earlier studies would obviate the need and benefit for ADT remains unclear. On the other hand, it is possible that combining HT with a dose-escalated RT regimen would increase even further the magnitude of the HT benefit. Two randomized trials are currently addressing that issue. The recently completed Quebec PCS III trial (principal investigator: Dr. A. Nabid) is a 3-arm study comparing short-term ADT plus 70 Gy, short-term ADT plus 76 Gy, and 76 Gy alone. The RTOG 08-15 trial (principal investigator: Dr. A.A. Martinez) is randomizing patients to 79.2 Gy with or without short-term ADT. Both trials are exclusively targeting patients with intermediate-risk disease. Until these trials are completed and reported, questions about the real benefit of HT in combination with high-dose RT remain unanswered.

3.4 Toxicity

Androgen deprivation has been associated with numerous side effects, including sexual dysfunction, gynecomastia, bone mineral loss, anemia, fatigue, muscular pain, hot flashes, metabolic complications, and potentially increased cardiovascular events [69–71]. The latter issue is a controversial one that is receiving increased attention in the decision-making process.

Some retrospective studies with large cohorts have reported increased risks of cardiovascular events and incident diabetes with the use of ADT [72,73]. Tsai *et al.* [74], using data from the CAPSURE database, demonstrated an increased risk of cardiovascular events for patients receiving ADT in the prostatectomy context, but interestingly, not for patients undergoing RT. A recent study from Ontario with more than 19,000 users of ADT found an increased risk of diabetes, but not an excess risk of myocardial infarction or sudden cardiac death [75]. A combined analysis by D'Amico *et al.* [76] of three published randomized trials showed that, in men more than 65 years of age, the use of short-term ADT did not change the overall rate of cardiac events; however, the time to develop fatal myocardial infarction was decreased. That study is limited by the small number of events (51 myocardial infarctions). Another single-institution study recently presented data on increased all-cause mortality for patients with pre-existing heart failure or a history of myocardial infarction who were receiving neoadjuvant ADT [77]. That subgroup of patients is likely the one that requires specific counselling when ADT is being considered.

Reanalyses of the RTOG randomized trials 92-02 [78], 86-10 [40], 85-31 [78], and 94-08 [38] and the EORTC 22961 [60] trial have not shown any significant differences in cardiovascular mortality between the experimental and the control arms. However, those studies might be underpowered to detect a difference for that endpoint, contributing to the current uncertainty on the issue.

The potential existence of a direct causal relationship between ADT and cardiovascular disease undoubtedly needs clarification, including the mechanisms that might be involved and whether the risk continues after cessation of ADT. Despite all the conflicting data, patients should be advised to undergo early screening to detect insulin resistance, diabetes, hyperlipidemia, and hypertension, and they should be counselled to maintain a healthy diet and regular physical activity.

4. CONCLUSIONS

In low-risk PCa, the benefit of combined HT and RT is not evident, and the routine use of combined therapy should be avoided. For patients harbouring high-risk disease, available level 1 evidence supports the combination of RT and HT. Major randomized trials suggest that ADT improves survival, and the combination of long-term ADT with RT is currently

considered the treatment of choice for high-risk patients. The optimal duration of HT in this population has yet to be determined, but strong evidence currently supports its use for at least 24 months. Intermediate-risk patients are a heterogeneous group in which the role of ADT is not well defined, particularly in the context of dose-escalated RT. Notably, previous randomized trials included patients with diverse risk factors treated with older RT modalities, suboptimal RT dose, and a variety of HT schedules and durations, making the role of ADT more controversial. The results of ongoing randomized trials will hopefully provide more definitive answers to some of the foregoing questions.

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6. CONFLICT OF INTEREST DISCLOSURES

All authors declare that no financial conflicts of interest exist.

7. REFERENCES

1. Haas GP, Delongchamps N, Brawley OW, Wang CY, de la Roza G. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *Can J Urol* 2008;15:3866–71.
2. Pasteau O. Traitement du cancer de la prostate par le radium. *Rev Mal Nutr* 1911:303–7.
3. Kuban DA, Thames HD, Levy LB, *et al.* Long-term multi-institutional analysis of stage T1–T2 prostate cancer treated with radiotherapy in the PSA era. *Int J Radiat Oncol Biol Phys* 2003;57:915–28.
4. Shipley WU, Thames HD, Sandler HM, *et al.* Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. *JAMA* 1999;281:1598–604.
5. Zagars GK, Pollack A, von Eschenbach AC. Prognostic factors for clinically localized prostate carcinoma: analysis of 938 patients irradiated in the prostate specific antigen era. *Cancer* 1997;79:1370–80.
6. Peters LJ. The ESTRO Regaud lecture. Inherent radiosensitivity of tumor and normal tissue cells as a predictor of human tumor response. *Radiother Oncol* 1990;17:177–90.
7. D'Amico AV, Matelski H, O'Leary M, Sussman B. Prostate-specific antigen-producing cells in the bone marrow of a patient with early-stage prostate cancer. *Urology* 1997;49:279–82.
8. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *J Urol* 2002;168:9–12.
9. Nesbit RM, Plumb RT. Prostatic carcinoma, follow-up on 795 patients treated prior to endocrine era and comparison of survival rates between these and patients treated by endocrine therapy. *Surgery* 1946;20:263–72.
10. de Voogt HJ, Pavone–Macaluso M, Smith PH, de Pauw M, Suciu S. Lessons from phase III-trials on the hormonal treatment of prostatic cancer. I: Results of EORTC-trials 30761 and 30762. *Prog Clin Biol Res* 1988;260:111–17.
11. Management of advanced cancer of prostate and bladder. Proceedings of a symposium on the tenth anniversary of EORTC, Leeds, England, October 3rd, 1986 and the Fifth Course in Urological Oncology, Erice, Sicily, November 28–December 4th, 1986. *Prog Clin Biol Res* 1988;260:1–658.
12. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000;355:1491–8.
13. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. *Lancet* 1995;346:265–9.
14. Zagars GK, Johnson DE, von Eschenbach AC, Hussey DH. Adjuvant estrogen following radiation therapy for stage C adenocarcinoma of the prostate: long-term results of a prospective randomized study. *Int J Radiat Oncol Biol Phys* 1988;14:1085–91.
15. Lamb DS, Denham JW, Mameghan H, *et al.* Acceptability of short term neo-adjuvant androgen deprivation in patients with locally advanced prostate cancer. *Radiother Oncol* 2003;68:255–67.
16. Tyrrell CJ, Payne H, See WA, *et al.* Bicalutamide ("Casodex") 150 mg as adjuvant to radiotherapy in patients with localised or locally advanced prostate cancer: results from the randomised Early Prostate Cancer Programme. *Radiother Oncol* 2005;76:4–10.
17. See WA, Tyrrell CJ. The addition of bicalutamide 150 mg to radiotherapy significantly improves overall survival in men with locally advanced prostate cancer. *J Cancer Res Clin Oncol* 2006;132(suppl 1):S7–16.
18. Lukka H, Warde P, Pickles T, Morton G, Brundage M, Souhami L. Controversies in prostate cancer radiotherapy: consensus development. *Can J Urol* 2001;8:1314–22.
19. Zietman AL, Prince EA, Nakfoor BM, Park JJ. Androgen deprivation and radiation therapy: sequencing studies using the Shionogi *in vivo* tumor system. *Int J Radiat Oncol Biol Phys* 1997;38:1067–70.
20. Zietman AL, Prince EA, Nakfoor BM, Shipley WU. Neoadjuvant androgen suppression with radiation in the management of locally advanced adenocarcinoma of the prostate: experimental and clinical results. *Urology* 1997;49:74–83.
21. Kaminski JM, Hanlon AL, Joon DL, Meistrich M, Hachem P, Pollack A. Effect of sequencing of androgen deprivation and radiotherapy on prostate cancer growth. *Int J Radiat Oncol Biol Phys* 2003;57:24–8.
22. Stewart GD, Ross JA, McLaren DB, Parker CC, Habib FK, Riddick AC. The relevance of a hypoxic tumour microenvironment in prostate cancer. *BJU Int* 2010;105:8–13.
23. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005;307:58–62.
24. Folkman J. Seminars in Medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med* 1995;333:1757–63.
25. Fukumura D, Jain RK. Tumor microvasculature and microenvironment: targets for anti-angiogenesis and normalization. *Microvasc Res* 2007;74:72–84.
26. Joseph IB, Isaacs JT. Potentiation of the antiangiogenic ability of linomide by androgen ablation involves down-regulation of vascular endothelial growth factor in human androgen-responsive prostatic cancers. *Cancer Res* 1997;57:1054–7.

27. Joseph IB, Nelson JB, Denmeade SR, Isaacs JT. Androgens regulate vascular endothelial growth factor content in normal and malignant prostatic tissue. *Clin Cancer Res* 1997;3:2507–11.
28. Weidner N, Carroll PR, Flax J, Blumenfeld W, Folkman J. Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. *Am J Pathol* 1993;143:401–9.
29. Borre M, Offersen BV, Nerstrom B, Overgaard J. Microvessel density predicts survival in prostate cancer patients subjected to watchful waiting. *Br J Cancer* 1998;78:940–4.
30. Mucci LA, Powolny A, Giovannucci E, *et al.* Prospective study of prostate tumor angiogenesis and cancer-specific mortality in the health professionals follow-up study. *J Clin Oncol* 2009;27:5627–33.
31. Okihara K, Watanabe H, Kojima M. Kinetic study of tumor blood flow in prostatic cancer using power Doppler imaging. *Ultrasound Med Biol* 1999;25:89–94.
32. Huang SF, Chang RF, Moon WK, Lee YH, Chen DR, Suri JS. Analysis of tumor vascularity using three-dimensional power Doppler ultrasound images. *IEEE Trans Med Imaging* 2008;27:320–30.
33. Milosevic M, Chung P, Parker C, *et al.* Androgen withdrawal in patients reduces prostate cancer hypoxia: implications for disease progression and radiation response. *Cancer Res* 2007;67:6022–5.
34. Milosevic M, Chung P, Toi A, *et al.* Androgen deprivation reduces hypoxia in human prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;66(suppl 3):S12.
35. Isaacs JT, Lundmo PI, Berges R, Martikainen P, Kyprianou N, English HF. Androgen regulation of programmed death of normal and malignant prostatic cells. *J Androl* 1992;13:457–64.
36. Roden AC, Moser MT, Tri SD, *et al.* Augmentation of T cell levels and responses induced by androgen deprivation. *J Immunol* 2004;173:6098–108.
37. Cooperberg MR, Broering JM, Litwin MS, *et al.* The contemporary management of prostate cancer in the United States: lessons from the cancer of the prostate strategic urologic research endeavor (CAPSURE), a national disease registry. *J Urol* 2004;171:1393–401
38. McGowan D, Hunt D, Jones C, *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.
39. 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.
40. Roach M 3rd, Bae K, Speight J, *et al.* Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. *J Clin Oncol* 2008;26:585–91.
41. Laverdiere J, Nabid A, De Bedoya LD, *et al.* The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2–T3 prostate cancer. *J Urol* 2004;171:1137–40.
42. 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.
43. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA* 2008;299:289–95.
44. 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.
45. Nguyen PL, Chen MH, Beard CJ, *et al.* Radiation with or without 6 months of androgen suppression therapy in intermediate- and high-risk clinically localized prostate cancer: a postrandomization analysis by risk group. *Int J Radiat Oncol Biol Phys* 2009;77:1046–52.
46. Roach M 3rd, Hanks G, Thames H Jr, *et al.* Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965–74.
47. Oefelein MG. Time to normalization of serum testosterone after 3-month luteinizing hormone-releasing hormone agonist administered in the neoadjuvant setting: implications for dosing schedule and neoadjuvant study consideration. *J Urol* 1998;160:1685–8.
48. Padula GD, Zelefsky MJ, Venkatraman ES, *et al.* Normalization of serum testosterone levels in patients treated with neoadjuvant hormonal therapy and three-dimensional conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;52:439–43.
49. 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.
50. Crook J, Ludgate C, Malone S, *et al.* Final report of multicenter Canadian phase III randomized trial of 3 versus 8 months of neoadjuvant androgen deprivation therapy before conventional-dose radiotherapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;73:327–33.
51. Alexander A, Crook J, Jones S, *et al.* Is biochemical response more important than duration of neoadjuvant hormone therapy before radiotherapy for clinically localized prostate cancer? an analysis of the 3- versus 8-month randomized trial. *Int J Radiat Oncol Biol Phys* 2010;76:23–30.
52. Pilepich MV, Caplan R, Byhardt RW, *et al.* Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. *J Clin Oncol* 1997;15:1013–21.
53. 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.
54. Bolla M, Gonzalez D, Warde P, *et al.* Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300.
55. 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.
56. Hanks GE, Pajak TF, Porter A, *et al.* Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003;21:3972–8.
57. 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.
58. Souhami L, Bae K, Pilepich M, Sandler H. Impact of the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy: a secondary analysis of RTOG 85-31. *J Clin Oncol* 2009;27:2137–43.
59. Pollack A, Salem N, Ashoori F, *et al.* Lack of prostate cancer radiosensitization by androgen deprivation. *Int J Radiat Oncol Biol Phys* 2001;51:1002–7.
60. 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.
61. D'Amico AV, Denham JW, Bolla M, *et al.* Short- vs long-term androgen suppression plus external beam radiation therapy and survival in men of advanced age with node-negative high-risk adenocarcinoma of the prostate. *Cancer* 2007;109:2004–10.
62. Haworth A, Kearvell R, Greer PB, *et al.* Assuring high quality treatment delivery in clinical trials—results from the Trans-Tasman Radiation Oncology Group (TROG) study 03.04 "RADAR" set-up accuracy study. *Radiother Oncol* 2009;90:299–306.
63. 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.
64. Peeters ST, Heemsbergen WD, Koper PC, *et al.* Dose–response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006;24:1990–6.
65. Sathya JR, Davis IR, Julian JA, *et al.* Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23:1192–9.
66. Dearnaley DP, Sydes MR, Graham JD, *et al.* Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;8:475–87.
67. Zietman AL, DeSilvio ML, Slater JD, *et al.* Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;294:1233–9.
68. Zietman AL. Correction: inaccurate analysis and results in a study of radiation therapy in adenocarcinoma of the prostate. *JAMA* 2008;299:898–9.
69. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *JAMA* 2005;294:238–44.
70. Alibhai SM, Gogov S, Allibhai Z. Long-term side effects of androgen deprivation therapy in men with non-metastatic prostate cancer: a systematic literature review. *Crit Rev Oncol Hematol* 2006;60:201–15.
71. Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J Clin Endocrinol Metab* 2005;90:6410–17.
72. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448–56.
73. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer* 2007;110:1493–500.
74. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst* 2007;99:1516–24.
75. Alibhai SM, Duong–Hua M, Sutradhar R, *et al.* Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J Clin Oncol* 2009;27:3452–8.
76. D'Amico AV, Denham JW, Crook J, *et al.* Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol* 2007;25:2420–5.
77. Nanda A, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. *JAMA* 2009;302:866–73.
78. Efstathiou JA, Bae K, Shipley WU, *et al.* Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *J Clin Oncol* 2009;27:92–9.

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