Risk stratification in the hormonal treatment of patients with prostate cancer

Matthew A. Uhlman, Judd W. Moul, Ping Tang, Danielle A. Stackhouse and Leon Sun

Ther Adv Med Oncol

(2009) 1(2) 79–94

DOI: 10.1177/
1758834009340164

© The Author(s), 2009.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Prostate cancer (PCa) is the most common type of cancer found in American men, other than skin cancer. The American Cancer Society estimates that there will be 186,320 new cases of prostate cancer in the United States in 2008. About 28,660 men will die of this disease this year and PCa remains the second-leading cause of cancer death in men. One in six men will get PCa during his lifetime and one in 35 will die of the disease. Today, more than 2 million men in the United States who have had PCa are still alive. The death rate for PCa continues to decline, chiefly due to early detection and treatment, and improved salvage therapy such as hormone therapy (HT). HT continues to be a mainstay for primary-recurrent PCa and locally-advanced PCa. However, HT is associated with many undesirable side effects including sexual dysfunction, osteoporosis and hot flashes, all of which can lead to decreased quality of life (QOL). These risks are seen in both long- and short-term HT regimens. Additionally, research in recent years has revealed trends related to clinico pathological variables and their predictive ability in HT outcomes. Awareness of the potential adverse effects, the risks associated with HT and the prognostic ability of clinical and pathological variables is important in determining optimal therapy for individual patients. A rigorous evaluation of the current scientific literature associated with HT was conducted with the goal of identifying the most favorable balance of benefits and risks associated with HT.

Keywords: prostate cancer, recurrence, survival, hormonal therapy, toxicity, risk factors, quality of life

Risks and benefits of hormonal therapy

Since Huggins and Hodges discovered that prostate cancer (PCa) cell growth is androgen dependent, hormonal therapy (HT) has been increasingly utilized for the treatment of PCa [Huggins and Hodges, 1972; Huggins, 1967; Huggins and Hodges, 1941]. Approximately 30% of the existing 2 million PCa patients receive HT in the context of adjuvant/neo-adjuvant therapy before or after radical prostatectomy (RP) or external radiotherapy (XRT) [Smith, 2007]. HT has become an increasingly common treatment for organ-confined PCa in the United States over the last decade [Barry *et al.* 2006; Cooperberg *et al.* 2003]. With this increase in popularity, patients are now receiving HT for extended periods of time. HT is not without risk, however, and is associated with numerous side effects including vasomotor flushing, loss of libido, erectile dysfunction, cognitive decline,

arterial stiffness, anemia, fatigue, gynecomastia, mastodynia, osteoporosis leading to fractures, obesity, sarcopenia, and cardiovascular disease [Isbarn *et al.* 2008; Michaelson *et al.* 2008; Higano, 2003]. More recently, metabolic complications including insulin resistance, diabetes, dyslipidemia and metabolic syndrome have been observed in patients receiving HT. These findings have led some to suggest they are potential explanations for the increased cardiovascular mortality seen in this population [Hakimian *et al.* 2008; Saigal *et al.* 2007; Tsai *et al.* 2007; Keating *et al.* 2006; Smith *et al.* 2006b; Yannucci *et al.* 2006], though some studies have found no increase in cardiovascular mortality for men on androgen deprivation therapy (ADT) [Efsthathiou *et al.* 2009]. Given the large side-effect profile of HT, it is understandable that HT is associated with decreased quality of life (QOL) [Fowler *et al.* 2002].

Correspondence to:
Judd W. Moul, MD
Professor and Chief,
Division of Urologic
Surgery and Duke
Prostate Center, Duke
University Medical Center,
PO Box 3707, Durham,
NC 27710
judd.moul@duke.edu

Matthew A. Uhlman
Ping Tang
Danielle A. Stackhouse
Leon Sun
Division of Urologic
Surgery and Duke
Prostate Center,
Department of Surgery,
Duke University Medical
Center, Durham, NC 27710

Prostate-specific antigen (PSA) recurrence

Patients with biochemical recurrence or PSA recurrence (PSAR), an increase in PSA to greater than 0.2 ng/ml following curative therapy, continue to be the main subjects utilizing HT as it has not been shown to be superior to current treatments as a primary therapy for PCa [Akaza *et al.* 2006]. Curative treatments such as radical prostatectomy (RP) are effective for clinically-localized PCa, however, up to 40% of men will have biochemical evidence of cancer progression, evident as a detectable serum PSA level within 10 years following initial treatment [Amling *et al.* 2000; Pound *et al.* 1999; Catalona and Smith, 1994; Zincke *et al.* 1994]. As a result, it is important to be familiar with the key risk factors for PSAR following curative treatment. Risk factors include age, race, clinical and pathological stage, Gleason score (GS), PSA and small prostate size [Khatami *et al.* 2007; Freedland *et al.* 2005; Moul *et al.* 2001].

With the growing number of patients on HT and limited data available on optimal treatment regimens, it is important to consider the risks and benefits associated with each therapeutic option. This article focuses on the risks and benefits associated with HT, as well as strategies for stratifying patients in order to achieve maximal benefits while effectively balancing risks.

Methods of HT

Castration remains the gold standard of HT. It is accomplished in one of two ways that have been shown to be equally effective – medical and surgical castration [Seidenfeld *et al.* 2000; Vogelzang *et al.* 1995; Kaisary *et al.* 1991]. Medical castration is accomplished through the administration of a luteinizing hormone-releasing hormone (LHRH) agonist, anti-androgen, LHRH pure-antagonist, complete androgen blockade (CAB, castration + anti-androgen) or triple androgen blockade (CAB + 5 α -reductase inhibitor). Other pharmacological options are available, but rarely utilized due to unacceptable clinical side effects [The Veterans Administration Co-Operative Urological Research Group, 1967] or decreased efficacy. Surgical castration on the other hand is accomplished through bilateral orchiectomy. Both medical and surgical castration achieve similar therapeutic goals, although they do so in different ways and, consequently, have different associated risks and benefits.

Medical castration

LHRH agonists

Since the introduction of LHRH agonists in the early 1980s, their use in the treatment of PCa has continued to increase. LHRH agonists work primarily through reducing active levels of androgens. Currently available LHRH agonists include leuporelin, goserelin, triptorelin, and buserelin. More recently, sustained-release formulations that require dosing every 1–12 months have become available. Today, LHRH agonists are the most common form of HT [Boccon-Gibod, 2005] and the most extensively studied.

Anti-androgens

Nonsteroidal anti-androgens are another popular form of HT, in large part due to the decreased sexual side effects as compared to LHRH agonists or orchiectomy [Dreicer, 2000]. Anti-androgens work by blocking androgen receptors, which keeps circulating androgen levels normal or increased. Currently available agents include flutamide, nilutamide and bicalutamide. With the lack of randomized controlled trials, limited recommendations for anti-androgen monotherapy exist.

Combined androgen blockade and triple androgen blockade

Combined androgen blockade (CAB) is a combination therapy which includes medical or surgical castration combined with an anti-androgen. It is also referred to as maximal androgen blockade (MAB).

CAB has been investigated in many different trials, but with conflicting results. In 1989, Crawford and colleagues with a cohort of 603 men with disseminated, untreated PCa, showed a 25% survival advantage (35.6 *vs* 28.3 months) in those receiving leuprolide with flutamide (CAB) *versus* those receiving leuprolide plus placebo [Crawford *et al.* 1989]. A decade later however, Eisenberger and colleagues found no difference in survival in 1387 men with metastatic PCa who were treated with castration +/- flutamide [Eisenberger *et al.* 1998]. More recently, a meta-analysis of 30 trials showed that, at 5 years, treatment with CAB *versus* castration was associated with a small, clinically insignificant survival advantage of 2–3% when compared to castration alone [Prostate Cancer Trialists' Collaborative Group, 2000]. These findings were confirmed in 2006 in a systematic review by Lukka *et al.* [Lukka *et al.* 2006]. Both studies questioned the benefit of

CAB given the increased side effects and potential decreased QOL associated with treatment. A recent review found more support for CAB, primarily due to a potential for more effective androgen blockade with bicalutamide [Klotz, 2008]. Currently, monotherapy through orchiectomy or LHRH agonist, rather than CAB is recommended for the treatment of men with recurrent PCa.

Triple androgen blockage (TAB) is CAB with the addition of a 5 α -reductase inhibitor. TAB has been studied far less than CAB. Initial results from Leibowitz and Tucker in 2001 showed TAB with finasteride maintenance to be promising [Leibowitz and Tucker, 2001]. However, little data has been published since with no trials supporting its use over the currently available therapies.

Pure LHRH antagonists

LHRH antagonists are one of the newer forms of HT and work by blocking LHRH receptors. The major advantage of these drugs is the absence of biochemical flare, a transient increase in testosterone associated with the initiation of androgen deprivation therapy (ADT). Abarelix, the first LHRH antagonist, was as effective as leuprolide at suppressing testosterone, but was taken off the market due to an increased rate of immediate-onset systemic allergic reactions [Trachtenberg *et al.* 2002; Mcleod *et al.* 2001; Tomera *et al.* 2001]. More recently, degarelix has been introduced and has not been associated with allergic reactions [Klotz *et al.* 2008]. To date there have been no long-term trials examining the efficacy of LHRH antagonists *versus* the currently available therapies.

Surgical castration

Bilateral orchiectomy as a treatment for advanced PCa was first investigated by Huggins and Hodges in a study of 21 patients with metastatic PCa. Of those treated, 15 had either subjective or objective improvement of pain or neurologic symptoms [Huggins and Hodges, 1941]. Orchiectomy is a relatively simple, minimally-invasive procedure that is easy to perform [Loblaw *et al.* 2007]. It remains the most popular HT method in developing countries [Deng *et al.* 2004]. However, with the advent of viable medical alternatives, and because of the physical and psychological discomforts and irreversibility of orchiectomy, surgical castration has fallen out of favor in developed countries [Mcleod, 2003; Clark *et al.* 2001].

The role of hormone therapy in prostate cancer

Hormone therapy as a primary therapy for localized prostate cancer

There is currently no evidence supporting the use of HT in patients with localized PCa. Iversen and colleagues in a randomized controlled trial with 1,218 patients showed that treatment with 150 mg/day of bicalutamide in men with early, nonmetastatic PCa did not significantly improve survival. In fact, a trend toward decreased overall survival was seen in the group receiving bicalutamide [Iversen *et al.* 2006]. The American Urological Association (AUA) guidelines state that primary ADT may be employed with the goal of providing symptomatic control of PCa for patients in whom definitive treatment with surgery or radiation is neither possible nor acceptable. Today, neither the AUA or the European Association of Urology (EAU) recommends the use of HT as primary therapy for PCa in patients with localized disease who are candidates for other treatment [Heidenreich *et al.* 2008; Thompson *et al.* 2007].

Hormone therapy as a primary therapy for locally advanced or metastatic disease

For patients with metastatic disease, HT has been shown to provide quality-of-life improvements including reduction in fractures, bone pain and ureteral obstruction [Huggins *et al.* 1941; Huggins, 1967]. A systematic review and meta-analysis of 24 single-therapy HT trials for men with advanced PCa showed no difference in survival between LHRH agonist and orchiectomy groups, though data showed a trend toward decreased survival in patients treated with anti-androgens [Seidenfeld *et al.* 2000]. This finding was confirmed by Tyrell and colleagues in a prospective trial including 1,453 men with locally-advanced or metastatic PCa. Treatment with bicalutamide *versus* castration was found to be less effective for patients with metastatic disease. No survival difference was seen for patients with locally-advanced disease [Tyrell *et al.* 1998]. The authors did point out the significant decrease in sexual side effects in patients treated with bicalutamide and that it could be used in patients for whom surgical and medical castration is not indicated or acceptable. Wirth and associates recently reported 7-year results from the Early Prostate Cancer program which randomized men to standard of care (RP, radiation or watchful waiting) $\pm$ bicalutamide. At 7 years,

men with locally-advanced disease receiving bicalutamide, showed a 34% reduction in progression-free survival, but no difference in overall survival [Wirth *et al.* 2007]. CAB has also been explored in patients with metastatic disease. In the largest trial to date, Eisenberger and colleagues found no difference in survival in 1,387 men with metastatic PCa who were treated with castration +/- flutamide [Eisenberger *et al.* 1998].

A number of other studies have examined the efficacy of HT in patients with locally-advanced or metastatic disease that looked at immediate *versus* delayed treatment delivery. These studies are discussed below. The AUA and EAU currently recommend treating patients with asymptomatic metastatic PCa with HT, however, the optimal time to initiate treatment is unknown. For patients with symptomatic metastatic PCa, HT should be initiated immediately.

Hormone therapy combined with radical prostatectomy

Neo-adjuvant therapy with prostatectomy. There is little evidence to suggest that neo-adjuvant LHRH agonists with RP are of any survival benefit. Boorjian and associates showed, in a retrospective trial of 507 men, 455 of which were treated with HT, that adjuvant HT decreased the risk of PSAR and local recurrence, but did not significantly affect overall survival [Boorjian *et al.* 2007]. Recently a large Cochrane meta-analysis demonstrated that neo-adjuvant HT (LHRH agonists and anti-androgens) can significantly improve adverse pathological characteristics including positive margins, and tumor stage, but does not improve overall survival [Kumar *et al.* 2006]. Currently, neo-adjuvant HT with RP is not recommended by the AUA or EAU.

Adjuvant therapy with prostatectomy. A number of trials have shown that adjuvant HT following prostatectomy does not increase survival as compared to prostatectomy alone. In one of the largest trials to date – the Early Prostate Cancer program – Wirth and colleagues showed that patients receiving adjuvant bicalutamide had no advantage in survival over those receiving placebo [Wirth *et al.* 2007]. In another retrospective trial by Siddiqui and colleagues, ADT following RP was associated with increased progression-free survival and cancer-specific survival. However, it was not found to increase overall survival [Siddiqui *et al.* 2008]. Finally, for patients

with lymph-node metastases, Boorjian and associates found that ADT was associated with a significantly reduced risk of PSAR and local recurrence, but did not demonstrate a survival advantage [Boorjian *et al.* 2007].

The only circumstance in which adjuvant HT with RP has been shown to increase survival was in a small study of 98 men with lymph-node metastases. The study assigned patients to immediate or delayed ADT and after nearly 12 years of follow up, found that those who received immediate HT had significantly increased overall survival [Messing *et al.* 2006]. The study has been criticized though due to its small size and lack of generalizability to the population at large.

Currently, there is no evidence to suggest that neoadjuvant or adjuvant HT with RP provides any overall survival benefit in patients without lymph-node metastases and as such, neither neo-adjuvant nor adjuvant HT with RP is currently recommended by the AUA or EAU. For patients with lymph-node positivity, the EAU recommends immediate ADT whereas the AUA does not address the situation in their guidelines.

Hormone therapy combined with radiation therapy

Neoadjuvant radiotherapy. ADT with radiotherapy has been shown to significantly increase overall survival in a number of studies. Bolla, in a randomized trial with a cohort of 415 men with locally-advanced PCa, showed that the addition of an LHRH agonist (goserelin) to radiotherapy significantly improved overall survival at 5 years (78 *versus* 62% with radiotherapy alone) [Bolla, 1997]. Pilepich and colleagues also found that the addition of an LHRH agonist to radiotherapy significantly decreased disease-specific death rates at 10 years in men with locally-advanced disease (16 *versus* 22%) [Pilepich *et al.* 2005]. Of particular interest was the finding that improved survival appeared preferentially in patients with a GS of ≥ 7 . Additionally, Iversen and colleagues showed that 150 mg/day of bicalutamide in addition to radiation therapy reduced the risk of death by 35% in men with locally-advanced disease. Additional studies have shown a survival advantage in men receiving neoadjuvant- or adjuvant-combined androgen blockade (LHRH agonist + anti-androgen) with radiotherapy.

Another study by D'amico and colleagues also demonstrated a survival advantage in men receiving adjuvant HT (LHRH agonist + anti-androgen) with radiotherapy [D'amico *et al.* 2004]. Additional studies have shown neoadjuvant HT with radiotherapy significantly increases overall survival [Denham *et al.* 2005; Laverdiere *et al.* 2004]. Currently, both the AUA and EAU recommend neo-adjuvant and adjuvant HT for patients with high-grade or locally-advanced PCa who will be receiving radiotherapy [Heidenreich *et al.* 2008; Thompson *et al.* 2007].

Hormone therapy combined with other treatment modalities for prostate cancer

HT is often given to patients before treatments such as brachytherapy to reduce the size of the prostate [Lee, 2002]. However, a number of studies have shown that neo-adjuvant ADT with brachytherapy does not lead to increased survival [Merrick *et al.* 2007; Machtens *et al.* 2006; Galalae *et al.* 2004]. One retrospective study found that men receiving neo-adjuvant ADT with brachytherapy had significantly reduced survival, but due to the nature of the study, the findings must be interpreted lightly [Beyer *et al.* 2005]. Currently, neither the AUA nor the EAU guidelines recommend the use of neo-adjuvant HT with brachytherapy.

Hormone therapy following PSA recurrence

Patients with PSAR continue to be the most common recipients of HT [Akaza *et al.* 2006]. However, there is little evidence guiding these decisions. Early studies demonstrated that androgen-deprivation therapy reduces metastatic complications including ureteral obstruction, bone pain and fractures [The Medical Research Council Prostate Cancer Working Party Investigators Group, 1997; The Veterans Administration Co-Operative Urological Research Group, 1967]. Although there has never been a survival advantage demonstrated with HT, it can provide significantly increased QOL to patients with metastatic disease. However, the majority of patients receiving HT do not have metastatic disease. HT is associated with significant side effects that can affect QOL negatively and, as a result, physicians are faced with questions of when to initiate treatment and on what schedule to continue it.

Immediate versus delayed therapy. For locally-advanced and metastatic PCa, there is much debate about the best time to start therapy.

Immediate or early therapy refers to the initiation of HT as soon as a patient's PSA begins to rise following surgery, whereas delayed therapy generally begins when clinical signs of metastatic disease are present. Only a few randomized trials for immediate *versus* delayed therapy exist today. The Medical Research Council, with a cohort of 983 men with locally-advanced or metastatic PCa, randomized men to immediate or delayed HT and found no survival difference between therapies. Patients receiving immediate therapy, however, did have significantly lower rates of pathological fractures, bone pain and ureteral obstruction [The Medical Research Council Prostate Cancer Working Party Investigators Group, 1997]. More recently, Moul and colleagues with the largest retrospective cohort to date with 1,352 patients, found that immediate therapy was associated with delayed clinical metastases in patients with a GS >7 or a PSA doubling time <12 months. No survival advantage was seen. A Cochrane review by Nair and colleagues concluded that immediate HT is associated with a small, but significant survival advantage at 10 years [Nair *et al.* 2002]. However, it also concluded that early therapy is associated with increased costs and more side-effects. Finally, a review by Messing and colleagues concluded that immediate HT may have a survival advantage for men with non-metastatic, lymph node positive disease [Messing *et al.* 2006]. Men with metastatic disease may not see a survival advantage, but will see improved QOL with HT.

Continuous versus intermittent therapy. As patients are undergoing HT for increasingly longer periods of time, providers are now faced with the challenge of how often to administer HT. Nearly all patients who undergo HT will eventually develop PCa that is resistant to therapy. This is termed castration-resistant PCa (CRPC) and currently there is little that physicians can do to treat the disease. A number of trials have been conducted comparing intermittent HT (IHT) with continuous HT (CHT). A number of trials in the past have concluded that IHT is no worse than CHT, but due to small sizes of the trials in question, limited recommendations have been made [Prapotnich *et al.* 2009; Peyromaure *et al.* 2005; De La Taille *et al.* 2003; Youssef *et al.* 2003]. A Cochrane review completed in 2007 found that there is not enough data to suggest that IHT is more effective than CHT for survival or disease progression and limited information suggests that

IHT may have slightly reduced adverse events [Conti *et al.* 2007]. A recently completed randomized trial by Calais Da Silva that included 626 men with locally-advanced or metastatic disease found that men receiving IHT *versus* CHT were not significantly different with respect to survival. The IHT group had more cancer deaths, but less cardiovascular deaths. QOL was no different while undergoing treatment, though men on IHT had significantly better sexual activity and the overall cost was significantly reduced in the IHT group.

Currently the AUA does not have definitive recommendations regarding treatment initiation-time or treatment intervals for HT following PSAR. The EAU guidelines suggest that a period of watchful waiting may be appropriate with a possibility of HT at a later time. They also state that lymph node-positive disease may be an indication for immediate HT, but they do not go so far as to recommend it. For intermittent *versus* continuous therapy, the EAU guidelines state that IHT may be acceptable for some patients, but that randomized trials are needed.

Risks associated with hormone therapy

HT continues to be a popular treatment option for men with recurrent or advanced PCa, however, the treatment is not without risks. Medical and surgical castration have been shown to be equally effective treatments for PCa [Vogelzang *et al.* 1995; Kaisary *et al.* 1991], but today, for multiple reasons, medical options are more often utilized. However, regardless of therapy choice, both forms of treatment have significant side effects. LHRH agonists and surgical castration both effectively reduce testosterone levels and as a result have a similar side-effect profile, though there have been limited reports on orchiectomy alone. In addition there is limited data on anti-androgens, which makes valid comparisons between treatments difficult. Even with limited data on these specific therapies, a great amount of research has been conducted looking at LHRH agonists and anti-androgens.

Biochemical flare

A side effect specific to LHRH agonists is the flare phenomenon. Before the 'resetting' of the anterior hypothalamic-pituitary-gonadal axis, stimulation of the anterior pituitary with a LHRH agonist results in a surge of increased testosterone. The flare reaction is not seen in patients treated with other forms of castration. Thompson and

associates demonstrated, in a review of 765 patients from 9 studies, that 10.9% of patients experienced a flare and 2% died [Thompson *et al.* 1990]. In patients with overt metastases who are at risk of developing symptoms associated with a surge in testosterone with initial LHRH agonist administration, anti-androgen therapy should precede or be co-administrated with the LHRH agonist and be continued in combination for at least 7 days [Schulze and Senge, 1990; Labrie *et al.* 1987]. An exception exists for patients at high risk of impending spinal cord compression, for whom surgical castration is recommended [Heidenreich *et al.* 2008].

Sexual side effects

Sexual side effects are the most common among patients undergoing HT. However, recent research has demonstrated differences in side-effect rates between HT with LHRH agonists and anti-androgens.

ADT. The side effects of LHRH agonists are comparable with those of castration, principally due to the reduction in testosterone levels to <50 ng/dl achieved by both therapies.

The list of side effects with HT is significant and patient considerations on QOL must be factored into any treatment decisions. Sexual side effects are reported at variables, but nonetheless there are high rates with castration. Decreased libido is reported in up to 90% of patients and erectile dysfunction levels vary among studies ranging between 15–72% [Diblasio *et al.* 2008; Potosky *et al.* 2001]. In one study, Potosky and colleagues reported that sexual function among a cohort of 431 men was impaired similarly in patients undergoing either surgical or medical castration. In the study, 63.6 and 58.0% of patients (surgical and medical castration respectively) reported 'no interest' in sexual activity following HT, up from 27.6 and 31.7% before treatment [Potosky *et al.* 2001].

Diblasio, with a cohort of 359 patients, found an erectile-dysfunction rate of only 14% of patients following HT, but did admit that under-reporting likely played a role in the number [Diblasio *et al.* 2008]. Fowler and colleagues, with a cohort of over 1,300 men who underwent radical prostatectomy with or without HT, found that men receiving HT were significantly more likely to have decreased libido (69 *versus* 29% had 'no sex drive within the last 30 days') and were

significantly more likely to have had no erections since surgery (72 *versus* 55%) [Fowler *et al.* 2002].

Anti-androgens. Despite conflicting studies, the number of men receiving oral anti-androgen therapy alone has grown, in part due to the presumed decrease in sexual side effects associated with therapy. One study by Iversen and colleagues showed men receiving anti-androgens were much more likely to maintain sexual interest (64%) *versus* men receiving ADT (30%) [Iversen *et al.* 1998]. See and Tyrrell found that patients given bicalutamide at a dose of 150 mg/day before radiotherapy had rates of impotence (12.7%) and decreased libido (4%) that were not statistically different from men receiving placebo. These results are much lower than reported rates for men undergoing more traditional ADT [See and Tyrrell, 2006].

Osteoporosis and fractures

As patients continue to receive HT for longer periods of time, osteoporosis has emerged as a significant risk of treatment.

ADT. ADT has been shown to increase the risk of osteoporosis and pathological fractures in multiple studies [Malcolm *et al.* 2007; Smith *et al.* 2006a; Shahinian *et al.* 2005; Preston *et al.* 2002]. Longer-term treatment with ADT, increased age (>70) at treatment initiation and CHT have all been shown to increase rates of osteoporosis and fractures [Malcolm *et al.* 2007]. Reported rates of osteoporosis vary widely within the literature, with a range of 7–23% [Malcolm *et al.* 2007; Shahinian *et al.* 2005]. Rates of fractures in patients on ADT also vary widely between studies, with a range of approximately 5–20% with fracture rates for control patients generally in the range of 0.7–12% [Malcolm *et al.* 2007; Smith *et al.* 2006a; Lopez *et al.* 2005; Shahinian *et al.* 2005; Oefelein *et al.* 2001; Hatano *et al.* 2000; Townsend *et al.* 1997]. Lopez and colleagues found a four-fold increase in fracture risk in patients on CAB [Lopez *et al.* 2005]. Shahinian and associates looking at a cohort of more than 50,000 men, found ADT was associated with a significant increase in osteoporosis (0.59–6.92% *versus* 0.46–3.59% for non-ADT patients) and fractures (3.41–19.37% *versus* 2.8–12.63%) [Shahinian *et al.* 2005].

A number of trials have shown that the administration of bisphosphonates during ADT can increase bone-mineral density (BMD). Yuen and colleagues in a review of 1,955 patients found bisphosphonate administration led to significant decreases in pain and skeletal events (fractures, spinal cord compression and bone surgery) [Yuen *et al.* 2006]. Others have demonstrated that taking pamidronate during HT reduces bone loss in the hip and lumbar spine [Diamond *et al.* 2001; Smith *et al.* 2001]. Perhaps the most important agent for overall skeletal health for men with PCa, with metastases or undergoing HT, is zoledronic acid. It has been shown to prevent bone loss in patients with locally-advanced PCa receiving HT [Polascik and Mouraviev, 2008; Ryan *et al.* 2006]. In addition, zoledronic acid has been shown to reduce the number of skeletal-related events (SRE) in men with CRPC [Polascik *et al.* 2005; Saad *et al.* 2004; 2002].

Anti-androgens. Anti-androgen therapy, unlike ADT, has not been shown to increase the risk of osteoporosis. A number of smaller trials have demonstrated reduced rates of osteoporosis with anti-androgen use *versus* ADT [Sieber *et al.* 2004; Smith *et al.* 2004; Tyrrell *et al.* 2003]. Wadhwa and colleagues in a prospective trial of 618 men randomized to LHRH agonist or anti-androgen, showed that men on anti-androgen, therapy maintained BMD whereas those taking a LHRH agonist had a significant loss. The exact mechanism through which anti-androgens may decrease the risk of osteoporosis is unknown, however, it is known that the drugs effectively block the effects of testosterone while allowing serum testosterone levels to remain normal or elevated. It has been suggested that the increased testosterone levels, through peripheral aromatization, may lead to higher levels of estrogen which in turn may slow the rate of bone loss [Verhelst *et al.* 1994]. Randomized trials are needed to confirm the effects of anti-androgens on osteoporosis, however preliminary findings are encouraging.

Metabolic issues

ADT is associated with significant body composition/metabolic changes including increased rates of metabolic syndrome, diabetes, hypercholesterolemia, hypertriglyceridemia, and coronary artery disease (CAD) [Kintzel *et al.* 2008; Braga-Basaria *et al.* 2006a, 2006b]. Increased body fat and reduced lean-muscle mass are well-known effects of ADT [Van Londen *et al.* 2008; Smith, 2004; Berruti *et al.* 2002; Chen *et al.* 2002] with fat

content increasing up to 20% in one study and lean body mass decreasing by 3.8%. Often these changes are evident in the first 3–6 months of ADT [Smith *et al.* 2006b; Berruti *et al.* 2002]. Keating and colleagues showed that ADT was associated with increased levels of diabetes (Hazard ratio (HR) = 1.44 for LHRH agonist and 1.34 for orchiectomy), but interestingly found that only treatment with a LHRH agonist, and not orchiectomy, was associated with increased risk for CAD, MI and sudden cardiac death [Keating *et al.* 2006]. Saigal and colleagues found that men receiving ADT for at least 1 year were at a 20% higher risk of serious cardiovascular morbidity than men not receiving ADT. They also found that risk began within 12 months of treatment initiation. Anti-androgen therapy has not been associated with significant metabolic side effects [Saigal *et al.* 2007].

Cognitive issues

As HT duration has increased, cognitive decline has become a more discussed potential side effect. Within the last decade a large number of studies have demonstrated the relationship between HT and subtle, but significant cognitive changes. A review performed by Nelson and associates showed the three cognitive areas that were affected most often by ADT were visuospatial abilities, working memory and executive functioning [Nelson *et al.* 2008]. To our knowledge, no large studies have examined anti-androgen therapy and cognitive decline.

Additional side effects

Gynecomastia and breast tenderness are the most commonly reported side effects of oral anti-androgen therapy alone with rates as high as 67.1 and 75.1%, respectively. ADT is generally associated with significantly lower rates with reports of gynecomastia and breast tenderness as low as 3.8 and 1.9% respectively [Iversen *et al.* 1998]. Potosky and colleagues reported gynecomastia rates of 24.9 and 9.7% for patients on LHRH agonists and receiving orchiectomy respectively [Potosky *et al.* 2001].

Hot flashes are another unpleasant, but common side effect of ADT with incidence rates ranging from 50–80% [Sharifi *et al.* 2005; Holzbeierlein *et al.* 2004; Higano, 2003; Chen *et al.* 2002; Potosky *et al.* 2001]. Up to 30% of men on ADT report hot flashes as the most debilitating side effect of therapy [Sharifi *et al.* 2005; Holzbeierlein *et al.* 2004; Chen *et al.* 2002].

Rates of hot flashes for medical and surgical castration patients are similar with some reports suggesting a slightly, but not statistically significant, reduced incidence in men receiving orchiectomy [Higano, 2003; Potosky *et al.* 2001; Sarosdy *et al.* 1999; Parmar *et al.* 1987]. Hot flashes are reported at much lower rates (10–15%) with anti-androgen therapy [See *et al.* 2006; Iversen *et al.* 1998].

Risk Stratification for hormone therapy

For many years, patients with PSAR have effectively fallen into their own category making further treatment stratification difficult. This is in large part due to a lack of randomized trials and the resultant dearth of prognostic data for patients who have initiated HT. As a result, knowing the optimal balance of risks and rewards is complicated. Some trials however have reported prognostic factors for men undergoing HT and though the trials are designed to look at different aspects of HT, themes have started to emerge.

Stratification factors for HT

Trials looking at the effects of HT are increasing in popularity as the treatment modality is becoming more utilized. To date, there have been no trials examining the effects of HT on subgroups of patients based on clinical or pathological characteristics (such as GS, PSA level, etc). However, as research efforts have increased, trends have started to emerge. These results and future trials may help physicians determine who will gain the most benefit from HT. Below is a summary of some of the factors found to be predictive of HT outcomes. A complete list of findings from trials is seen in Table 1.

PSA-related factors. While PSA levels have been shown to predict PSAR and prostate cancer specific mortality (PCSM), few studies have specifically examined the predictive power of PSA as it relates to HT. A number of studies have found that PSA-related factors including pretreatment PSA, PSA nadir level and PSA doubling time (PSADT) may identify patients at higher risk of HT failure or PCSM. In a large study that looked at 1,076 patients with metastatic PCa, Glass and colleagues found that a PSA < 65 ng/ml significantly predicted 5-year survival in patients receiving HT [Glass *et al.* 2003]. A number of smaller studies have demonstrated that factors such as a higher PSA nadir after initiation of HT and PSADT < 12 months predict worse outcomes for men on HT [Choueiri *et al.* 2009; Chung *et al.*

Table 1. Summary of risk stratification results from previous hormone therapy (HT) trials.

Paper	HT therapy	Findings
<i>HT after curative therapy</i>		
Glass [Glass <i>et al.</i> 2003]	Orchiectomy +/- flutamide	GS < 8 and PSA < 65 ng/ml significantly predicted 5 year survival
Thompson [Thompson <i>et al.</i> 2001]	Orchiectomy +/- flutamide	African American race, GS > 8 and bone pain significantly predicted lower 5 year survival
Chung [Chung <i>et al.</i> 2008]	Orchiectomy, LHRH agonists, anti-androgens or CAB	High PSA at HT initiation, GS > 7, PSA nadir > 0.9 ng/ml significantly predicted PCSM
Rodrigues [Rodrigues <i>et al.</i> 2006]	ADT - No further definition given	PSA nadir > 0.2 ng/ml and GS > 7 significantly predicted PCSM
Choueiri [Choueiri <i>et al.</i> 2009]	Orchiectomy, LHRH agonists and CAB	PSA time to nadir < 6 months, GS > 7, PSA nadir > 0.2 ng/ml predicted shorter overall survival
Ross [Ross <i>et al.</i> 2008]	Orchiectomy, LHRH agonist and CAB	With metastases GS > 7 predicted shorter time to progression. Without metastases PSA predicted shorter time to progression. Previous ADT predicted shorter time to progression for both.
Porter [Porter <i>et al.</i> 2007]	Orchiectomy or LHRH agonist	Pathologic stage > T3 predicted PCa specific mortality
Scholz [Scholz <i>et al.</i> 2007]	LHRH agonist +/- anti-androgen	PSA nadir > 0.05 ng/ml and PSADT < 12 months were predictive of PCSM
Banez [Banez <i>et al.</i> 2009]	Flutamide with or without finasteride	PSA > 4 ng/ml before HT initiation was predictive of disease progression
Hussain [Hussain <i>et al.</i> 2006]	CAB	PSA nadir > 4 ng/ml after 7 months of ADT, GS > 7 and bony pain was significantly predictive of decreased survival.
<i>HT as primary treatment</i>		
Janoff [Janoff <i>et al.</i> 2005]	Orchiectomy or LHRH agonists	Age < 70 and GS >= 6 were found to be at higher risk for treatment failure
Graff [Graff <i>et al.</i> 2007]	Orchiectomy, LHRH agonists and CAB	GS >= 7, PSA >= 20 ng/ml and a low number of co-morbidities significantly predicting PCSM
<i>Intermittent versus continuous HT</i>		
Prapotnich [Prapotnich <i>et al.</i> 2009]	CAB after primary failure	Age < 60, PSA > 100 and GS > 7 were predictive of mortality in patients undergoing intermittent CAB
Irani [Irani <i>et al.</i> 2008]	CAB	Disease progression was associated with PSA and GS. GS was predictive of PCSM
<i>Immediate versus delayed HT</i>		
Studer [Studer <i>et al.</i> 2008]	Orchiectomy or LHRH agonist	PSADT = < 12 months and PSA > 50 ng/ml at treatment initiation were predictive of increase mortality for patients who underwent delayed ADT
Tenenholz [Tenenholz <i>et al.</i> 2007]	Orchiectomy, LHRH agonist, anti-androgen, or DES	PSA > 15 ng/ml, PSADT ≤ 7 months, log of PSADT and log PSA were predictive of overall survival. Log of PSADT was significantly predictive of disease specific survival.
Moul [Moul <i>et al.</i> 2004]	LHRH agonist, orchiectomy or CAD	HT delayed clinical metastases in patients with GS > 7 and PSADT = < 12 months
ADT, androgen deprivation therapy; CAB, complete androgen blockade; DES, diethylstilbestrol; GS, Gleason score; LHRH, luteinizing hormone-releasing hormone; PCSM, prostate cancer-specific mortality; PSA, prostate specific antigen; PSADT, PSA doubling time.		

2008; Studer *et al.* 2008; Scholz *et al.* 2007; Tenenholz *et al.* 2007].

Finally, Hussain, with a cohort of 1,345 men with metastatic disease undergoing intermittent or continuous ADT, found that a PSA nadir between 0.2–4 ng/ml and PSA nadir < 0.2 ng/ml were significant predictors of survival (HR = 0.30 and HR = 0.17 respectively) [Hussain *et al.* 2006].

Though no specific levels have been determined, data show that a higher PSA level at treatment

time, a higher PSA nadir following treatment and a faster PSADT (both before definitive treatment and HT) are all correlated with worse outcomes.

Gleason score. GS is another factor that is consistently found to predict negative outcomes both before definitive treatment and HT. A GS > 7 is generally regarded as aggressive disease. Prapotnich and colleagues in a nonrandomized trial including 566 men on ADT, found that a GS > 7 was predictive of increased mortality [Prapotnich *et al.* 2009]. Additionally, Ross

found that a $GS > 7$ was correlated with shorter time to progression in patients undergoing ADT with metastatic disease, but not in those without metastases [Ross *et al.* 2008]. Finally, in a large trial, Glass and colleagues found that a $GS > 7$ was a significant predictor of decreased survival in patients undergoing HT [Glass *et al.* 2003].

As with previously described factors, there is no GS that has been definitively shown to predict worse outcomes. However, increasing GS, especially above 7, has consistently been associated with decreased survival and treatment failure.

Race. Being of African American (AA) race is a known predictor of PSAR, but limited studies have examined race as it pertains to HT outcomes. In a large trial of 1,263 men with metastatic PCa who received orchiectomy with or without flutamide, Thompson and colleagues found that AA race was a significant predictor of decreased overall survival [Thompson *et al.* 2001]. More studies are needed to determine why this relationship exists.

Summary of risk factors

Based on a limited number of trials reporting factors predictive of success or failure with HT as well as a shortage of randomized trials, it is difficult to make definitive recommendations as to which patients are best suited for HT. Nevertheless, emerging trends from available trials suggest that distinct clinico-pathological characteristics, including elevated PSA, rapid PSADT, high PSA nadir following therapy and $GS > 7$, may give prognostic information as to which patients are likely to gain the most benefit from HT. This information and future findings are likely to lead to risk stratification guidelines for men undergoing HT for PCa.

Conclusion

HT continues to be a common treatment option for recurrent PCa and locally advanced PCa. Both long- and short-term treatment courses are associated with many undesirable side effects which can lead to decreased QOL. There are only a few circumstances in which HT is clearly indicated:

- (1) For patients with high risk disease that are undergoing radiation therapy;
- (2) To shrink the prostate before brachytherapy (though there has been no survival advantage demonstrated); and

- (3) To palliate symptoms in patients with metastatic PCa [Heidenreich *et al.* 2008; Thompson *et al.* 2007].

Treatment with anti-androgens has been shown to be inferior to ADT for patients with metastatic disease [Tyrrell *et al.* 1998]. For patients with recurrent disease after definitive treatment, there is little data suggesting a survival advantage from the use of HT, however much data exists to support the palliate ability of the treatment.

Both LHRH agonists and anti-androgens are associated with significant side effects. Treatments with anti-androgens have much lower rates of sexual side effects, hot flashes and osteoporosis. Anti-androgens are also not known to cause biochemical flare. Treatment with ADT results in lower rates of gynecomastia and breast tenderness.

Emerging research has shown that HT may be associated with increased rates of metabolic and cardiac complications as well as cognitive declines. CAB has been shown to produce a small, but significant increase in overall survival, but cost considerations and side effects should be taken into consideration. Treatment with LHRH antagonists and TAB are not well studied.

Questions remain as to the best time to initiate treatment, the optimal duration, the best treatment schedule and most importantly, which patients are the most likely to benefit from HT. Patient stratification based on clinical and pathological factors remains ambiguous and though results from trials are limited, some trends have started to materialize. Patients undergoing HT and with characteristics including a $PSADT \leq 12$ months, $GS > 7$, PSA nadir > 0.2 ng/ml and elevated PSA at time of HT may be at increased risk of disease progression and ultimately PCSM, though additional studies are needed to confirm these initial findings.

In the end, communication is paramount in determining optimal therapy for individual patients. Before initiation of HT, clinicians should carefully consider the factors that have been shown to correlate with poor HT outcomes, and patients should be made aware of the potential adverse effects and risks associated with different HT treatment options. This combination of efforts gives patients and providers the best chance at achieving the optimal balance of risk and benefit.

Acknowledgement

The author Matthew Uhlman wishes to acknowledge the NIH Grant TL1 RR 024126.

Conflict of Interest Statement

None declared.

References

- Akaza, H., Homma, Y., Usami, M., Hirao, Y., Tsushima, T., Okada, K. *et al.* (2006) Efficacy of primary hormone therapy for localized or locally advanced prostate cancer: results of a 10-year follow-up. *BJU Int* 98: 573–579.
- Amling, C.L., Blute, M.L., Bergstralh, E.J., Seay, T.M., Slezak, J. and Zincke, H. (2000) Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. *J Urol* 164: 101–105.
- Banez, L.L., Blake, G.W., Mcleod, D.G., Crawford, E.D. and Moul, J.W. (2009) Combined low-dose flutamide plus finasteride vs low-dose flutamide monotherapy for recurrent prostate cancer: a comparative analysis of two phase ii trials with a long-term follow-up. *BJU Int* [Epub ahead of print].
- Barry, M.J., Delorenzo, M.A., Walker-Corkery, E.S., Lucas, F.L. and Wennberg, D.C. (2006) The rising prevalence of androgen deprivation among older american men since the advent of prostate-specific antigen testing: A population-based cohort study. *BJU Int* 98: 973–978.
- Berruti, A., Dogliotti, L., Terrone, C., Cerutti, S., Isaia, G., Tarabuzzi, R. *et al.* (2002) Changes in bone mineral density, lean body mass and fat content as measured by dual energy X-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol* 167: 2361–2367; discussion 2367.
- Beyer, D.C., McKeough, T. and Thomas, T. (2005) Impact of short course hormonal therapy on overall and cancer specific survival after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 61: 1299–1305.
- Boccon-Gibod, L. (2005) Optimizing hormone therapy in advanced disease. *European Urology Supplement* 4: 21–29.
- Bolla, M. (1997) Combination of radiotherapy and hormonotherapy in locally advanced cancers of the prostate. *Cancer Radiother* 1: 439–442.
- Boorjian, S.A., Thompson, R.H., Siddiqui, S., Bagniewski, S., Bergstralh, E.J., Karnes, R.J. *et al.* (2007) Long-term outcome after radical prostatectomy for patients with lymph node positive prostate cancer in the prostate specific antigen era. *J Urol* 178: 864–870; discussion 870–861.
- Braga-Basaria, M., Dobs, A.S., Muller, D.C., Carducci, M.A., John, M., Egan, J. *et al.* (2006a) Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol* 24: 3979–3983.
- Braga-Basaria, M., Muller, D.C., Carducci, M.A., Dobs, A.S. and Basaria, S. (2006b) Lipoprotein profile in men with prostate cancer undergoing androgen deprivation therapy. *Int J Impot Res* 18: 494–498.
- Catalona, W.J. and Smith, D.S. (1994) 5-year tumor recurrence rates after anatomical radical retropubic prostatectomy for prostate cancer. *J Urol* 152: 1837–1842.
- Chen, Z., Maricic, M., Nguyen, P., Ahmann, F.R., Bruhn, R. and Dalkin, B.L. (2002) Low bone density and high percentage of body fat among men who were treated with androgen deprivation therapy for prostate carcinoma. *Cancer* 95: 2136–2144.
- Choueiri, T.K., Xie, W., D'amico, A.V., Ross, R.W., Hu, J.C., Pomerantz, M. *et al.* (2009) Time to Prostate-specific antigen nadir independently predicts overall survival in patients who have metastatic hormone-sensitive prostate cancer treated with androgen-deprivation therapy. *Cancer* 115: 981–987.
- Chung, C.S., Chen, M.H., Cullen, J., Mcleod, D., Carroll, P. and D'amico, A.V. (2008) Time to prostate-specific antigen nadir after androgen suppression therapy for postoperative or postradiation psa failure and risk of prostate cancer-specific mortality. *Urology* 71: 136–140.
- Clark, J.A., Wray, N.P. and Ashton, C.M. (2001) Living with treatment decisions: Regrets and quality of life among men treated for metastatic prostate cancer. *J Clin Oncol* 19: 72–80.
- Conti, P.D., Atallah, A.N., Arruda, H., Soares, B.G., El Dib, R.P. and Wilt, T.J. (2007) Intermittent versus continuous androgen suppression for prostatic cancer. *Cochrane Database Syst Rev* CD005009.
- Cooperberg, M.R., Grossfeld, G.D., Lubeck, D.P. and Carroll, P.R. (2003) National practice patterns and time trends in androgen ablation for localized prostate cancer. *J Natl Cancer Inst* 95: 981–989.
- Crawford, E.D., Eisenberger, M.A., Mcleod, D.G., Spaulding, J.T., Benson, R., Dorr, F.A. *et al.* (1989) A Controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 321: 419–424.
- D'amico, A.V., Manola, J., Loffredo, M., Renshaw, A.A., Dellacroce, A. and Kantoff, P.W. (2004) 6-Month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *Jama* 292: 821–827.
- De La Taille, A., Zerbib, M., Conquy, S., Amsellem-Ouazana, D., Thiounn, N., Flam, T.A. *et al.* (2003) Intermittent androgen suppression in patients with prostate cancer. *BJU Int* 91: 18–22.
- Deng, J.H., Yang, L.P., Wang, L.S. and Zhou, D.F. (2004) Effect of androgen deprivation therapy on bone

- mineral density in prostate cancer patients. *Asian J Androl* 6: 75–77.
- Denham, J.W., Steigler, A., Lamb, D.S., Joseph, D., Mameghan, H., Turner, S. *et al.* (2005) 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* 6: 841–850.
- Diamond, T.H., Winters, J., Smith, A., De Souza, P., Kersley, J.H., Lynch, W.J. *et al.* (2001) The antiosteoporotic efficacy of intravenous pamidronate in men with prostate carcinoma receiving combined androgen blockade: A double blind, randomized, placebo-controlled crossover study. *Cancer* 92: 1444–1450.
- Diblasio, C.J., Malcolm, J.B., Derweesh, I.H., Womack, J.H., Kincade, M.C., Mancini, J.G. *et al.* (2008) Patterns of sexual and erectile dysfunction and response to treatment in patients receiving androgen deprivation therapy for prostate cancer. *BJU Int* 102: 39–43.
- Dreicer, R. (2000) The evolving role of hormone therapy in advanced prostate cancer. *Cleve Clin J Med* 67: 720–722, 725–726.
- Efstathiou, J.A., Bae, K., Shipley, W.U., Hanks, G.E., Pilepich, M.V., Sandler, H.M. *et al.* (2009) Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: Rtog 85–31. *J Clin Oncol* 27: 92–99.
- Eisenberger, M.A., Blumenstein, B.A., Crawford, E.D., Miller, G., Mcleod, D.G., Loehrer, P.J. *et al.* (1998) Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med* 339: 1036–1042.
- Fowler Jr, F.J., McNaughton Collins, M., Walker Corkery, E., Elliott, D.B. and Barry, M.J. (2002) The impact of androgen deprivation on quality of life after radical prostatectomy for prostate carcinoma. *Cancer* 95: 287–295.
- Freedland, S.J., Isaacs, W.B., Platz, E.A., Terris, M.K., Aronson, W.J., Amling, C.L. *et al.* (2005) Prostate size and risk of high-grade, advanced prostate cancer and biochemical progression after radical prostatectomy: A search database study. *J Clin Oncol* 23: 7546–7554.
- Galalae, R.M., Martinez, A., Mate, T., Mitchell, C., Edmundson, G., Nuernberg, N. *et al.* (2004) Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HdR-Bt) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 58: 1048–1055.
- Glass, T.R., Tangen, C.M., Crawford, E.D. and Thompson, I. (2003) Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. *J Urol* 169: 164–169.
- Graff, J.N., Mori, M., Li, H., Garzotto, M., Penson, D., Potosky, A.L. *et al.* (2007) Predictors of overall and cancer-free survival of patients with localized prostate cancer treated with primary androgen suppression therapy: results from the prostate cancer outcomes study. *J Urol* 177: 1307–1312.
- Hakimian, P., Blute Jr, M., Kashanian, J., Chan, S., Silver, D., Shabsigh, R. (2008) Metabolic and cardiovascular effects of androgen deprivation therapy. *BJU Int* 102: 1509–1514.
- Hatano, T., Oishi, Y., Furuta, A., Iwamuro, S. and Tashiro, K. (2000) Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. *BJU Int* 86: 449–452.
- Heidenreich, A., Aus, G., Bolla, M., Joniau, S., Matveev, V.B., Schmid, H.P. *et al.* (2008) Eau guidelines on prostate cancer. *Eur Urol* 53: 68–80.
- Higano, C.S. (2003) Side effects of androgen deprivation therapy: Monitoring and minimizing toxicity. *Urology* 61: 32–38.
- Holzbeierlein, J.M., McLaughlin, M.D. and Thrasher, J.B. (2004) Complications of androgen deprivation therapy for prostate cancer. *Curr Opin Urol* 14: 177–183.
- Huggins, C. (1967) Endocrine-induced regression of cancers. *Cancer Res* 27: 1925–1930.
- Huggins, C., Stevens, R.E. and Hodges, C.V. (1941) Studies on prostatic cancer, II: The effect of castration on advance prostatic carcinoma of the prostate gland. *Arch Surg* 43: 209–228.
- Huggins, C. and Hodges, C.V. (1972) Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *CA Cancer J Clin* 22: 232–240.
- Hussain, M., Tangen, C.M., Higano, C., Schelhammer, P.F., Faulkner, J., Crawford, E.D. *et al.* (2006) Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: Data from southwest oncology group trial 9346 (Int-0162). *J Clin Oncol* 24: 3984–3990.
- Irani, J., Celhay, O., Hubert, J., Bladou, F., Ragni, E., Trape, G. *et al.* (2008) Continuous versus six months a year maximal androgen blockade in the management of prostate cancer: a randomised study. *Eur Urol* 54: 382–391.
- Isbarn, H., Boccon-Gibod, L., Carroll, P.R., Montorsi, F., Schulman, C., Smith, M.R. *et al.* (2008) Androgen deprivation therapy for the treatment of prostate cancer: Consider both benefits and risks. *Eur Urol* 55: 62–75.
- Iversen, P., Johansson, J.E., Lodding, P., Kylmala, T., Lundmo, P., Klarskov, P. *et al.* (2006) Bicalutamide 150 Mg in addition to standard care for patients with early non-metastatic prostate cancer: Updated results from the scandinavian prostate cancer period group-6 study after a median

- follow-up period of 7.1 years. *Scand J Urol Nephrol* 40: 441–452.
- Iversen, P., Tyrrell, C.J., Kaisary, A.V., Anderson, J.B., Baert, L., Tammela, T. *et al.* (1998) Casodex (Bicalutamide) 150-Mg monotherapy compared with castration in patients with previously untreated non-metastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. *Urology* 51: 389–396.
- Janoff, D.M., Peterson, C., Mongoue-Tchokote, S., Peters, L., Beer, T.M., Wersinger, E.M. *et al.* (2005) Clinical outcomes of androgen deprivation as the sole therapy for localized and locally advanced prostate cancer. *BJU Int* 96: 503–507.
- Kaisary, A.V., Tyrrell, C.J., Peeling, W.B. and Griffiths, K. (1991) Comparison of Lhrh Analogue (Zoladex) with orchiectomy in patients with metastatic prostatic carcinoma. *Br J Urol* 67: 502–508.
- Keating, N.L., O'Malley, A.J. and Smith, M.R. (2006) Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 24: 4448–4456.
- Khatami, A., Aus, G., Damber, J.E., Lilja, H., Lodding, P. and Hugosson, J. (2007) Psa doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: Results from the european randomized study of screening for prostate cancer, Sweden section. *Int J Cancer* 120: 170–174.
- Kintzel, P.E., Chase, S.L., Schultz, L.M. and O'Rourke, T.J. (2008) Increased risk of metabolic syndrome, diabetes mellitus, and cardiovascular disease in men receiving androgen deprivation therapy for prostate cancer. *Pharmacotherapy* 28: 1511–1522.
- Klotz, L. (2008) Maximal androgen blockade for advanced prostate cancer. *Best Pract Res Clin Endocrinol Metab* 22: 331–340.
- Klotz, L., Boccon-Gibod, L., Shore, N.D., Andreou, C., Persson, B.E., Cantor, P. *et al.* (2008) 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* 102: 1531–1538.
- Kumar, S., Shelley, M., Harrison, C., Coles, B., Wilt, T.J. and Mason, M.D. (2006) Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. *Cochrane Database Syst Rev* CD006019.
- Labrie, F., Dupont, A., Belanger, A. and Lachance, R. (1987) Flutamide eliminates the risk of disease flare in prostatic cancer patients treated with a luteinizing hormone-releasing hormone agonist. *J Urol* 138: 804–806.
- Laverdiere, J., Nabid, A., De Bedoya, L.D., Ebacher, A., Fortin, A., Wang, C.S. *et al.* (2004) 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* 171: 1137–1140.
- Lee, W.R. (2002) The role of androgen deprivation therapy combined with prostate brachytherapy. *Urology* 60: 39–44; discussion 44.
- Leibowitz, R.L. and Tucker, S.J. (2001) Treatment of localized prostate cancer with intermittent triple androgen blockade: Preliminary results in 110 consecutive patients. *Oncologist* 6: 177–182.
- Loblaw, D.A., Virgo, K.S., Nam, R., Somerfield, M.R., Ben-Josef, E., Mendelson, D.S. *et al.* (2007) 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* 25: 1596–1605.
- Lopez, A.M., Pena, M.A., Hernandez, R., Val, F., Martin, B. and Riancho, J.A. (2005) Fracture risk in patients with prostate cancer on androgen deprivation therapy. *Osteoporos Int* 16: 707–711.
- Lukka, H., Waldron, T., Klotz, L., Winquist, E. and Trachtenberg, J. (2006) Maximal androgen blockade for the treatment of metastatic prostate cancer—a systematic review. *Curr Oncol* 13: 81–93.
- Machtens, S., Baumann, R., Hagemann, J., Warszawski, A., Meyer, A., Karstens, J.H. *et al.* (2006) Long-term results of interstitial brachytherapy (Ldr-Brachytherapy) in the treatment of patients with prostate cancer. *World J Urol* 24: 289–295.
- Malcolm, J.B., Derweesh, I.H., Kincade, M.C., Diblasio, C.J., Lamar, K.D., Wake, R.W. *et al.* (2007) Osteoporosis and fractures after androgen deprivation initiation for prostate cancer. *Can J Urol* 14: 3551–3559.
- McLeod, D., Zinner, N., Tomera, K., Gleason, D., Fotheringham, N., Campion, M. *et al.* (2001) A phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. *Urology* 58: 756–761.
- McLeod, D.G. (2003) Hormonal therapy: Historical perspective to future directions. *Urology* 61: 3–7.
- Merrick, G.S., Butler, W.M., Wallner, K.E., Galbreath, R.W., Allen, Z.A., Adamovich, E. *et al.* (2007) Androgen deprivation therapy does not impact cause-specific or overall survival in high-risk prostate cancer managed with brachytherapy and supplemental external beam. *Int J Radiat Oncol Biol Phys* 68: 34–40.
- Messing, E.M., Manola, J., Yao, J., Kiernan, M., Crawford, D., Wilding, G. *et al.* (2006) Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 7: 472–479.
- Michaelson, M.D., Cotter, S.E., Gargollo, P.C., Zietman, A.L., Dahl, D.M. and Smith, M.R. (2008) Management of complications of prostate cancer treatment. *CA Cancer J Clin* 58: 196–213.
- Moul, J.W., Connelly, R.R., Lubeck, D.P., Bauer, J.J., Sun, L., Flanders, S.C. *et al.* (2001) Predicting risk of

- prostate specific antigen recurrence after radical prostatectomy with the center for prostate disease research and cancer of the prostate strategic urologic research endeavor databases. *J Urol* 166: 1322–1327.
- Nair, B., Wilt, T., Macdonald, R. and Rutks, I. (2002) Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. *Cochrane Database Syst Rev* CD003506.
- Nelson, C.J., Lee, J.S., Gamboa, M.C. and Roth, A.J. (2008) Cognitive effects of hormone therapy in men with prostate cancer: A review. *Cancer* 113: 1097–1106.
- Oefelein, M.G., Ricchuiti, V., Conrad, W., Seftel, A., Bodner, D., Goldman, H. *et al.* (2001) Skeletal fracture associated with androgen suppression induced osteoporosis: The clinical incidence and risk factors for patients with prostate cancer. *J Urol* 166: 1724–1728.
- Parmar, H., Edwards, L., Phillips, R.H., Allen, L. and Lightman, S.L. (1987) Orchiectomy versus long-acting D-Trp-6-Lhrh in advanced prostatic cancer. *Br J Urol* 59: 248–254.
- Peyromaure, M., Delongchamps, N.B., Debre, B. and Zerbib, M. (2005) Intermittent androgen deprivation for biologic recurrence after radical prostatectomy: Long-term experience. *Urology* 65: 724–729.
- Pilepich, M.V., Winter, K., Lawton, C.A., Krisch, R.E., Wolkov, H.B., Movsas, B. *et al.* (2005) Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III rtog 85–31. *Int J Radiat Oncol Biol Phys* 61: 1285–1290.
- Polascik, T.J., Given, R.W., Metzger, C., Julian, S.R., Vestal, J.C., Karlin, G.S. *et al.* (2005) Open-label trial evaluating the safety and efficacy of zoledronic acid in preventing bone loss in patients with hormone-sensitive prostate cancer and bone metastases. *Urology* 66: 1054–1059.
- Polascik, T.J. and Mouraviev, V. (2008) Zoledronic acid in the management of metastatic bone disease. *Ther Clin Risk Manag* 4: 261–268.
- Porter, C.R., Gallina, A., Kodama, K., Gibbons, R.P., Correa Jr, R., Perrotte, P. *et al.* (2007) Prostate cancer-specific survival in men treated with hormonal therapy after failure of radical prostatectomy. *Eur Urol* 52: 446–452.
- Potosky, A.L., Knopf, K., Clegg, L.X., Albertsen, P.C., Stanford, J.L., Hamilton, A.S. *et al.* (2001) Quality-of-life outcomes after primary androgen deprivation therapy: Results from the prostate cancer outcomes study. *J Clin Oncol* 19: 3750–3757.
- Pound, C.R., Partin, A.W., Eisenberger, M.A., Chan, D.W., Pearson, J.D. and Walsh, P.C. (1999) Natural history of progression after psa elevation following radical prostatectomy. *Jama* 281: 1591–1597.
- Prapotnich, D., Cathelineau, X., Rozet, F., Barret, E., Mombet, A., Cathala, N. *et al.* (2009) A 16-year clinical experience with intermittent androgen deprivation for prostate cancer: Oncological results. *World J Urol* [Epub ahead of print].
- Preston, D.M., Torrens, J.I., Harding, P., Howard, R.S., Duncan, W.E. and Mcleod, D.G. (2002) Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer Prostatic Dis* 5: 304–310.
- Prostate Cancer Trialists' Collaborative Group (2000) Maximum androgen blockade in advanced prostate cancer: An overview of the randomised trials. *Lancet* 355: 1491–1498.
- Ross, R.W., Xie, W., Regan, M.M., Pomerantz, M., Nakabayashi, M., Daskivich, T.J. *et al.* (2008) Efficacy of Androgen Deprivation Therapy (Adt) in patients with advanced prostate cancer: Association between gleason score, prostate-specific antigen level, and prior Adt exposure with duration of Adt effect. *Cancer* 112: 1247–1253.
- Ryan, C.W., Huo, D., Demers, L.M., Beer, T.M. and Lacerna, L.V. (2006) Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. *J Urol* 176: 972–978; discussion 978.
- Saad, F., Gleason, D.M., Murray, R., Tchekmedyian, S., Venner, P., Lacombe, L. *et al.* (2002) A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 94: 1458–1468.
- Saad, F., Gleason, D.M., Murray, R., Tchekmedyian, S., Venner, P., Lacombe, L. *et al.* (2004) Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 96: 879–882.
- Saigal, C.S., Gore, J.L., Krupski, T.L., Hanley, J., Schonlau, M. and Litwin, M.S. (2007) Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer* 110: 1493–1500.
- Sarosdy, M.F., Schellhammer, P.F., Soloway, M.S., Vogelzang, N.J., Crawford, E.D., Presti, J. *et al.* (1999) Endocrine effects, efficacy and tolerability of a 10.8-Mg depot formulation of goserelin acetate administered every 13 weeks to patients with advanced prostate cancer. *BJU Int* 83: 801–806.
- Scholz, M., Lam, R., Strum, S., Jennrich, R., Johnson, H. and Trilling, T. (2007) Prostate-cancer-specific survival and clinical progression-free survival in men with prostate cancer treated intermittently with testosterone-inactivating pharmaceuticals. *Urology* 70: 506–510.
- Schulze, H. and Senge, T. (1990) Influence of different types of antiandrogens on luteinizing hormone-releasing hormone analogue-induced testosterone surge in patients with metastatic carcinoma of the prostate. *J Urol* 144: 934–941.
- See, W.A. and Tyrrell, C.J. (2006) The addition of bicalutamide 150 Mg to radiotherapy significantly

- improves overall survival in men with locally advanced prostate cancer. *J Cancer Res Clin Oncol* 132(Suppl 1): S7–16.
- Seidenfeld, J., Samson, D.J., Hasselblad, V., Aronson, N., Albertsen, P.C., Bennett, C.L. *et al.* (2000) Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. *Ann Intern Med* 132: 566–577.
- Shahinian, V.B., Kuo, Y.F., Freeman, J.L. and Goodwin, J.S. (2005) Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 352: 154–164.
- Sharifi, N., Gulley, J.L. and Dahut, W.L. (2005) Androgen deprivation therapy for prostate cancer. *Jama* 294: 238–244.
- Siddiqui, S.A., Boorjian, S.A., Inman, B., Bagniewski, S., Bergstralh, E.J. and Blute, M.L. (2008) Timing of androgen deprivation therapy and its impact on survival after radical prostatectomy: A matched cohort study. *J Urol* 179: 1830–1837; discussion 1837.
- Sieber, P.R., Keiller, D.L., Kahnoski, R.J., Gallo, J. and Mcfadden, S. (2004) Bicalutamide 150 Mg maintains bone mineral density during monotherapy for localized or locally advanced prostate cancer. *J Urol* 171: 2272–2276, quiz 2435.
- Smith, M.R. (2004) Changes in fat and lean body mass during androgen-deprivation therapy for prostate cancer. *Urology* 63: 742–745.
- Smith, M.R. (2007) Androgen deprivation therapy for prostate cancer: New concepts and concerns. *Curr Opin Endocrinol Diabetes Obes* 14: 247–254.
- Smith, M.R., Boyce, S.P., Moyneur, E., Duh, M.S., Raut, M.K. and Brandman, J. (2006a) Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. *J Urol* 175: 136–139; discussion 139.
- Smith, M.R., Goode, M., Zietman, A.L., McGovern, F.J., Lee, H. and Finkelstein, J.S. (2004) Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: Effects on bone mineral density and body composition. *J Clin Oncol* 22: 2546–2553.
- Smith, M.R., Lee, H. and Nathan, D.M. (2006b) Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 91: 1305–1308.
- Smith, M.R., McGovern, F.J., Zietman, A.L., Fallon, M.A., Hayden, D.L., Schoenfeld, D.A. *et al.* (2001) Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N Engl J Med* 345: 948–955.
- Studer, U.E., Collette, L., Whelan, P., Albrecht, W., Casselman, J., De Reijke, T. *et al.* (2008) Using psa to guide timing of androgen deprivation in patients with T0-4 N0-2 M0 prostate cancer not suitable for local curative treatment (Eortc 30891). *Eur Urol* 53: 941–949.
- Tenenholz, T.C., Shields, C., Ramesh, V.R., Tercilla, O. and Hagan, M.P. (2007) Survival benefit for early hormone ablation in biochemically recurrent prostate cancer. *Urol Oncol* 25: 101–109.
- The Medical Research Council Prostate Cancer Working Party Investigators Group (1997) Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the medical research council trial. *Br J Urol* 79: 235–246.
- The Veterans Administration Co-Operative Urological Research Group (1967) Treatment and survival of patients with cancer of the prostate. *Surg Gynecol Obstet* 124: 1011–1017.
- Thompson, I., Tangen, C., Tolcher, A., Crawford, E., Eisenberger, M. and Moinpour, C. (2001) Association of african-american ethnic background with survival in men with metastatic prostate cancer. *J Natl Cancer Inst* 93: 219–225.
- Thompson, I., Thrasher, J.B., Aus, G., Burnett, A.L., Canby-Hagino, E.D., Cookson, M.S. *et al.* (2007) Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol* 177: 2106–2131.
- Thompson, I.M., Zeidman, E.J. and Rodriguez, F.R. (1990) Sudden death due to disease flare with luteinizing hormone-releasing hormone agonist therapy for carcinoma of the prostate. *J Urol* 144: 1479–1480.
- Tomera, K., Gleason, D., Gittelman, M., Moseley, W., Zinner, N., Murdoch, M. *et al.* (2001) The Gonadotropin-releasing hormone antagonist abarelix depot versus luteinizing hormone releasing hormone agonists leuprolide or goserelin: Initial results of endocrinological and biochemical efficacies in patients with prostate cancer. *J Urol* 165: 1585–1589.
- Townsend, M.F., Sanders, W.H., Northway, R.O. and Graham Jr, S.D. (1997) Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate carcinoma. *Cancer* 79: 545–550.
- Trachtenberg, J., Gittleman, M., Steidle, C., Barzell, W., Friedel, W., Pessis, D. *et al.* (2002) A phase 3, multicenter, open label, randomized study of abarelix versus leuprolide plus daily antiandrogen in men with prostate cancer. *J Urol* 167: 1670–1674.
- Tsai, H.K., D'amico, A.V., Sadetsky, N., Chen, M.H. and Carroll, P.R. (2007) Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst* 99: 1516–1524.
- Tyrrell, C.J., Blake, G.M., Iversen, P., Kaisary, A.V. and Melezinek, I. (2003) The Non-steroidal antiandrogen, bicalutamide ('Casodex'), may preserve bone mineral density as compared with castration: Results of a preliminary study. *World J Urol* 21: 37–42.
- Tyrrell, C.J., Kaisary, A.V., Iversen, P., Anderson, J.B., Baert, L., Tammela, T. *et al.* (1998) A Randomised

comparison of 'Casodex' (Bicalutamide) 150 Mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. *Eur Urol* 33: 447–456.

Van Londen, G.J., Levy, M.E., Perera, S., Nelson, J.B. and Greenspan, S.L. (2008) Body composition changes during androgen deprivation therapy for prostate cancer: A 2-year prospective study. *Crit Rev Oncol Hematol* 68: 172–177.

Verhelst, J., Denis, L., Van Vliet, P., Van Poppel, H., Braeckman, J., Van Cangh, P. *et al.* (1994) Endocrine profiles during administration of the new non-steroidal anti-androgen casodex in prostate cancer. *Clin Endocrinol (Oxf)* 41: 525–530.

Vogelzang, N.J., Chodak, G.W., Soloway, M.S., Block, N.L., Schellhammer, P.F., Smith Jr, J.A. *et al.* (1995) Goserelin versus orchiectomy in the treatment of advanced prostate cancer: Final results of a randomized trial. zoladex prostate study group. *Urology* 46: 220–226.

Wirth, M., Tyrrell, C., Delaere, K., Sanchez-Chapado, M., Ramon, J., Wallace, D.M.

et al. (2007) Bicalutamide (Casodex) 150 Mg plus standard care in early non-metastatic prostate cancer: Results from early prostate cancer trial 24 at a median 7 years' follow-up. *Prostate Cancer Prostatic Dis* 10: 87–93.

Yannucci, J., Manola, J., Garnick, M.B., Bhat, G. and Bubley, G.J. (2006) The effect of androgen deprivation therapy on fasting serum lipid and glucose parameters. *J Urol* 176: 520–525.

Youssef, E., Tekyi-Mensah, S., Hart, K., Bolton, S. and Forman, J. (2003) Intermittent androgen deprivation for patients with recurrent/metastatic prostate cancer. *Am J Clin Oncol* 26: e119–123.

Yuen, K.K., Shelley, M., Sze, W.M., Wilt, T. and Mason, M.D. (2006) Bisphosphonates for advanced prostate cancer. *Cochrane Database Syst Rev* CD006250.

Zincke, H., Oesterling, J.E., Blute, M.L., Bergstralh, E.J., Myers, R.P. and Barrett, D.M. (1994) Long-term (15 years) results after radical prostatectomy for clinically localized (Stage T2c or Lower) prostate cancer. *J Urol* 152: 1850–1857.

Visit SAGE journals online
<http://tam.sagepub.com>

SAGE JOURNALS
Online