# Hormone therapy in the management of prostate cancer: evidence-based approaches

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***Abstract*:** Hormonal therapy has been the standard for advanced prostate cancer for over 60 years. Recently, the utility of androgen ablation through various means has been demonstrated for earlier stages of disease. In particular, the strongest evidence to date involves the use of hormonal therapy in combination with radiation therapy. In this article we review the basic concepts in hormonal ablation for prostate cancer and review the evidence-based studies that support the use of hormonal therapy in early stage prostate cancer.

***Keywords*:** prostate cancer, hormonal therapy, androgen deprivation therapy, combined androgen blockade

## Introduction

Prostate cancer (CaP) is the most commonly diagnosed solid tumor in men and the second leading cause of cancer death in males in the United States. CaP will continue to become an increasingly important healthcare issue in the coming years as the average life span of a male in the US continues to increase, and treatment of other chronic cormorbidities such as diabetes and cardiovascular disease continue to improve. By the year 2030, it is expected that the percentage of men above the age of 65 years will comprise almost 20% of the US population, an important age range for CaP management issues [Population Division, U.S. Census Bureau, 2010]. More importantly, the robust favorable long-term survival in low-risk CaP has become even more pronounced in recent years because prostate-specific antigen (PSA) testing has led to cancer diagnosis at an earlier point of the disease course and meaning that men are alive longer with their disease. On the other hand, death from locally advanced CaP still remains a challenging field. Those at greatest risk are men with stage T3–T4 cancer, pretreatment PSA $>20$ ng/ml, and Gleason score of $\geq 8$. Multiple studies are now demonstrating that men with adverse risk features who are treated in a multimodality fashion at the time of initial diagnosis are demonstrating improved overall CaP survival based on many large, prospective, randomized trials [Gomella, 2007; Sandler, 2004].

While traditionally hormonal therapy has been used only for metastatic disease, new applications that utilize hormonal therapy in earlier stages appear to be making a difference in CaP. The hormone responsive nature of prostate carcinoma provides an additional strategy to primary therapy alone by which clinical management may lead to improved long-term outcomes. Randomized, controlled, phase III clinical trials have examined the efficacy of immediate androgen deprivation therapy (ADT) as adjunctive therapy to prostatectomy and radiation therapy in men with unfavorable localized or locally advanced CaP with generally improved outcomes [Seruga and Tannock, 2008]. National data sets such as Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) support the fact that there has been an increasing use of strategies such as early hormone therapy in nonmetastatic disease [Cooperberg *et al.* 2003]. Given emerging data about the potential harms of ADT, the need is growing to define the optimal duration of ADT plus external beam radiotherapy for patients with locally advanced CaP. Testimony to the evolution in the treatment of locally advanced CaP is apparent through the impetus of designing randomized trials, as the urologic field pushes on to practice evidence-based medicine. The focus of this article is to highlight those trials that may help the clinician to develop the optimal regimen for the patient diagnosed with locally advanced CaP.

## Forms of hormonal manipulation and hormonal suppression

Hormone therapy, also described as ADT or androgen suppression therapy (AST), allows for a decrease in serum testosterone in an effort to slow down the growth of CaP. Multiple

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medications and strategies have been used to induce castrate serum levels of testosterone or to interfere with its function. One of earliest methods described in the 1940s by Huggins and Hodges was bilateral orchiectomy [Huggins and Hodges, 1941]. Surgical castration results in an effective reduction of circulating testosterone within a few hours, and still remains an underutilized method in the treatment of advanced CaP.

Several nonsurgical options exist in achieving hormonal suppression. Diethylstilbestrol (DES), a semisynthetic estrogen compound, was one of the first nonsurgical options for the treatment of CaP. At one time a first-line hormonal therapy, its widespread use has been limited due to significant cardiovascular and thromboembolic toxicity. Cyproterone acetate (CPA) is a steroidal, progestational antiandrogen that blocks the androgen-receptor interaction and reduces serum testosterone through a weak antigonadotropic action. CPA is also associated with a high rate of cardiovascular complications, and is not available in the United States.

The introduction of the luteinizing hormone-releasing hormone (LHRH) agonists, the two most commonly used in studies discussed in this article being leuprolide and goserelin, revolutionized the treatment of advanced CaP. After an initial surge of luteinizing hormone (LH)/follicle-stimulating hormone (FSH) and subsequently testosterone, constant exposure to treatment by LHRH agonists results in down-regulation of receptors in the pituitary gland. As a consequence, a decrease in testosterone production is observed from inhibition of FSH and LH release. Monotherapy with LHRH androgen deprivation results in a decline of 90% of circulating testosterone. Ten per cent of circulating testosterone is still present in castrated men due to peripheral conversion of circulating adrenal steroids to testosterone. To achieve maximal androgen blocklade (MAB), combined therapy with nonsteroidal antiandrogens (NSAAs) bicalutamide, flutamide, and nilutamide has also become an accepted option. NSAAs work by blocking the action of testosterone through the inhibition of the prostatic nuclear uptake of androgen. Ketoconazole also has been shown to be a useful second-line treatment in patients with advanced CaP, but its widespread use is limited by concerns regarding liver toxicity.

Degarelix is one of the new, modified gonadotropin-releasing hormone antagonists. Unlike the standard LHRH agonists, degarelix is a direct LHRH antagonist, and thus avoids the flare phenomenon. This compound was recently compared with leuprolide in a phase III randomized trial [Klotz *et al*. 2008]. Testosterone levels were suppressed significantly faster with degarelix than with leuprolide, with nearly all patients achieving castrate levels by day 3 of treatment. In addition, degarelix resulted in a significantly faster reduction in PSA level. Long-term disease control rates are not yet available.

## Hormonal therapy and radiation

There are several proposed theories on the synergism of hormone therapy with radiation. *In-vitro* models have shown a radiation-sensitizing effect of ADT. Joon and colleagues reported a supra-additive apoptosis with combination therapy in an in vivo study using Dunning rat prostate tumors. This synergism between the two modalities to maximize the apoptotic pathway for cellular death has been extended to treating CaP clinically [Joon *et al*. 1997]. Zietman and colleagues rationalized several reasons for combination therapy including cytoreduction by androgen ablation leaving fewer cancer cells for radiation therapy to eradicate [Zietman *et al*. 1997]. In addition, it has been hypothesized that hormone therapy may serve as a sensitizing agent, where preradiation therapy androgen ablation may result in a smaller prostate with better blood flow and less necrotic tissue or hypoxic regions, which are radioresistant. In addition to the potential antitumor synergy between androgen ablation and radiation therapy, there may be some usefulness in preradiation therapy androgen ablation to shrink the prostate. A smaller prostate target would then allow smaller radiation fields and limit radiation exposure and toxicity to adjacent tissues such as the bladder and rectum. The optimal duration of neoadjuvant androgen deprivation to achieve maximal prostate shrinkage appears to be 3 months for most prostates, but longer therapy up to 6 months in duration can achieve greater shrinkage in larger glands. A median volume reduction of 31% is achieved regardless of initial prostate size [Langenhuijsen *et al*. 2010].

A retrospective review by D'Amico and colleagues demonstrated the benefit of neoadjuvant hormone therapy (NHT) for locally advanced CaP. Estimates of 5-year PSA outcome after

radiation therapy with or without NHT were not statistically different among low-risk patients ($p = 0.09$), whereas intermediate- and high-risk patients treated with radiation therapy plus ADT had significantly better outcomes than those treated with radiation therapy alone ($p = 0.001$ and $p = 0.009$, respectively) [D'Amico *et al.* 2000]. Subsequently, several prospective randomized trials were published confirming the benefit of NHT to radiation.

The vast majority of clinical trials using the combination of hormonal therapy and radiotherapy have been performed in patients with locally advanced CaP. One of the first trials to investigate the use of NHT in combination with radiotherapy was the Radiation Therapy Oncology Group (RTOG) 86-10 study [Pilepich *et al.* 2001]. This study used a relatively short course of hormonal therapy (4 months) in patients with locally advanced disease. Patients were randomized to receive either a combination of goserelin, an LHRH analog, and flutamide, an oral antiandrogen, beginning 2 months prior to initiation of radiotherapy and for another 2 months during radiotherapy, or receiving radiotherapy alone. To be eligible for this trial, patients had to have clinical stage T2–T4 cancers with bulky disease as determined by a palpable tumor with dimensions of 25 $cm^2$ or greater. Since this study was performed before conformal therapy became widely used, standard radiation therapy was used at a dose of 65–70 Gy. At a median of 8 years of follow up, this study demonstrated improved local control rates (42% *versus* 30%), a decreased incidence of distant metastases (34% *versus* 45%), increased disease-free survival (33% *versus* 21%) and decreased cancer-specific mortality (23% *versus* 31%) for the combination radiotherapy–hormonal therapy group, respectively. Although overall survival favored the combination therapy arm (53% *versus* 44%) this difference did not reach statistical significance. Long-term follow up of 10 years confirmed initial findings: improved disease-specific mortality (23% *versus* 36%; $p = 0.01$), lower incidence of disease metastasis (35% *versus* 47%), disease-free survival (11% *versus* 3%) and biochemical failure (65% *versus* 80%) [Roach *et al.* 2008]. Among the study cohort, patients with a Gleason score of 6 or less appeared to benefit from the short course of hormone replacement therapy (HRT), whereas patients with a higher Gleason score did not experience the same benefit, perhaps indicating that patients with high risk disease had micrometastatic disease that was not affected by a short course of androgen ablation.

The use of short-term ADT in the neoadjuvant and adjuvant settings was also investigated in the recently reported RTOG 94-13 trial [Roach *et al.* 2003]. In addition to attempting to clarify the timing of NHT, this study evaluated the added benefit of extending the radiation field to include the whole pelvis (WPRT) rather than just the prostate only radiation (PORT) in patients with potential involvement of pelvic lymph nodes. Patients were randomized to radiation therapy to the pelvic lymph nodes and prostate or radiation therapy to the prostate alone and androgen ablation 4 months in duration beginning 2 months before radiation therapy (as in RTOG 86-10) or 4 months of androgen ablation beginning immediately following radiation therapy. The first randomization tested for a benefit of pelvic lymph node irradiation and the second randomization tested for biological interaction between radiation therapy and hormonal treatment. The results of the study demonstrated a benefit to combination therapy but only when WPRT was used in combination with NHT. An update of this trial with longer follow up continued to demonstrate that when NHT is used in conjunction with radiation therapy, WPRT yields a better progression-free survival than PORT. It also showed that combined NHT and WPRT offered overall improved survival than WPRT with short-term adjuvant hormonal treatment [Lawton *et al.* 2007].

Milecki and colleagues also recently published their experience with WPRT [Milecki *et al.* 2009]. The purpose of the trial was to study whether the use of NHT combined with WPRT for high-risk CaP patients was associated with increased survival benefit over PORT only. High-risk CaP patients were randomized to either NHT with WPRT and long-term ADT or PORT with long-term ADT. The 5-year actuarial cause-specific survival (CSS) rate was 90% compared with 79% favoring WPRT. In addition, the biochemical progression-free survival (bPFS) rate was 52% *versus* 40% for the WPRT group. However, overall survival did not reach a statistical significance at the 5-year follow-up, 89% *versus* 78%, for WPRT *versus* PORT, respectively. Both the RTOG 94-13 and Milecki and colleagues trials imply a synergistic effect between radiation and hormonal therapy on

micrometastatic disease in the pelvic lymph nodes and stress the importance of beginning hormonal therapy prior to the initiation of radiotherapy in patients with high-risk disease.

Clearly, if the goal is to minimize microscopic disease, perhaps a longer period of NHT might further improve outcome. The use of longer courses of hormonal therapy before radiotherapy has been investigated in two randomized trials. The Australian Trans-Tasman Radiation Oncology Group 96.01 trial was designed to determine whether 3 months or 6 months of androgen deprivation given before and during radiotherapy improves outcomes for patients with locally advanced CaP [Denham *et al*. 2005]. Compared with patients assigned no androgen deprivation, those assigned 3 months treatment had significantly improved local failure, biochemical failure-free survival, disease-free survival, and freedom from salvage treatment as illustrated in previous trials. Similarly, compared with no NHT, 6 months of androgen deprivation significantly improved similar outcomes. However, no difference in outcome was seen between the 3- and 6-month groups. A recently reported Canadian phase III randomized trial compared 3 months *versus* 8 months of NHT (flutamide and goserelin) combined with radiation therapy (66 Gy) in 378 patients with CaP of all risk groups [Crook *et al*. 2009]. While there was no difference in 7-year disease-free survival or cancer-specific survival rates between the two randomized arms, improved disease-free survival was noted in high-risk patients (71% *versus* 42%, $p = 0.01$). The disease-free survival rate at 5 years was improved for the high-risk patients in the 8-month arm (71% *versus* 42%). These studies suggest the possibility that longer courses of neoadjuvant ADT may be beneficial, particularly in patients with high-risk cancers.

While RTOG 86-10 and 94-13 used relatively short courses of hormonal therapy, subsequent randomized trials have examined short-term *versus* long-term ADT, finding that longer-term use improved outcomes. A landmark study performed by the European Organization for Research and Treatment of Cancer (EORTC) was the first study to demonstrate a survival advantage to the combination of radiotherapy and long-term hormonal therapy. The initial report of this trial demonstrated a significant survival benefit for those receiving the 3 years of hormonal therapy [Bolla *et al*. 1997]. The most recent update of this trial showed a persistent and impressive overall survival advantage with a hazard ratio of 0.51 for the combination therapy arm [Bolla *et al*. 2002]. At 5 years, the long-term androgen ablation arm of the study was superior to the radiation therapy only arm in overall survival rate (78% *versus* 62%) and CSS rate (94% *versus* 79%). This study was the first to show that a survival advantage could be realized when combined therapy is used for patients with locally advanced tumors and a high risk for micrometastatic disease.

Two additional RTOG trials also investigated the use of long-term ADT in patients with locally advanced CaP. RTOG 85-31 was designed to evaluate lifelong adjuvant androgen ablation combined with radiation therapy for clinical T3 or N positive disease *versus* radiation therapy and delayed androgen ablation [Pilepich *et al*. 2005]. Hormonal therapy was begun in the last week of radiotherapy and continued indefinitely. Adjuvant therapy improved all clinical endpoints, including improving 10-year overall survival from 39% to 49%. While there was no survival advantage seen in patients with lower-grade (Gleason 2–6) tumors, a significant advantage was seen for patients with higher-grade (Gleason 7–10) cancers (52% *versus* 42% for Gleason 7, $p = 0.026$, and 38% *versus* 24% for Gleason 8–10, $p = 0.0061$).

Another pivotal RTOG trial addressing the potential advantage of long-term hormonal therapy in higher-risk disease was the RTOG 92-02 trial [Horwitz *et al*. 2008]. RTOG 92-02 randomized 1500 patients with T3 or bulky T2c lesions to short-term androgen ablation (4 months as in RTOG 86-10) and radiation therapy or to long-term androgen ablation and radiation therapy, consisting of 2 years of adjuvant androgen ablation following radiation therapy. At 10 years, the group on the long-term regimen showed significant improvement over the short-term regimen for disease-free survival (13.2% *versus* 22.5%, $p = 0.0001$), disease-specific survival (83.9% *versus* 88.7%, $p = 0.0042$), local progression (22.2% *versus* 12.3%, $p = 0.0001$), distant metastasis (22.8% *versus* 14.8%, $p = 0.0001$) and biochemical failure (68.1% *versus* 51.9%, $p = 0.0001$). No overall survival advantage had been noted between the two groups; however, a subset analysis of Gleason score 8–10 cancers had significantly better overall survival with longer androgen deprivation. Randomized, controlled

**Table 1.** Summary of randomized controlled trials evaluating a combination of radiation and hormone therapy for nonmetastatic CaP [Horwitz *et al.* 2008; Pilepich *et al.* 2005, 2001; Bolla *et al.* 2002].

| Clinical trial | Eligibility | Treatment | % Cause-specific survival (years) | *p*-value | % Overall survival (years) | *p*-value |
|---|---|---|---|---|---|---|
| RTOG 86-10 | Bulky T2–T4 + primary tumor greater than 25 $cm^2$ on DRE | No androgen ablation, short-term androgen ablation (goserelin 3.6 mg/month + flutamide 250 mg/day for 4 months beginning 2 months before radiation therapy) | 69 (8), 77 (8) | 0.05 | 44 (8), 53 (8) | 0.10 |
| EORTC 22863 | cT1–T2 + WHO grade 3 or cT3–4, any grade | No androgen ablation, long-term androgen ablation (goserelin 3.6 mg/month for 3 years beginning on radiation therapy day 1, cyproterone acetate for the first 30 days) | 79 (5), 94 (5) | 0.0001 | 62 (5), 78 (5) | 0.0002 |
| RTOG 85-31 | cT3 or pos regional lymph nodes or following RP if pos margins +/or seminal vesicles | No androgen ablation (goserelin at relapse), long-term androgen ablation (goserelin 3.6 mg/months beginning radiation therapy last week + continuing indefinitely) | 78 (10), 83 (10) | 0.0053 | 38 (10), 53 (10) | 0.0043 |
| RTOG 92-02 | T2c–T4 (55% T3–T4) | Short-term androgen ablation as in RTOG 86-10, long-term androgen ablation as in RTOG 86-10, followed by goserelin 3.6 mg/month for 24 months | 91 (5), 95 (5) | 0.006 | 78 (5), 80 (5) | 0.73 |

DRE, digital rectal examination; RTOG, Radiation Therapy Oncology Group.

trials evaluating a combination of radiation and hormone therapy for nonmetastatic CaP are summarized Table 1.

Bolla and colleagues recently published their experience with the use of radiotherapy plus long-term *versus* short term androgen suppression in the treatment of locally advanced CaP [Bolla *et al.* 2009]. Accruing nearly 1100 patients, patients were randomized to radiotherapy plus 6 months of androgen suppression prior to radiation *versus* an additional 2.5 years of LHRH agonist after undergoing radiation therapy. The 5-year overall mortality significantly favored long-term hormonal suppression (15.2% *versus* 19.0%, respectively) with an observed hazard ratio of 1.42.

The benefit of long-term hormonal therapy in high-risk CaP patients has been demonstrated in several studies, but the evidence for the benefit of combination therapy in patients with lower risk disease is not so well replicated. The most widely cited evidence to justify androgen therapy in intermediate-risk patients was reported by D'Amico and colleagues, who performed a retrospective study of 1586 men treated with conformal radiation therapy with or without short-term (6-month) androgen ablation therapy [D'Amico *et al.* 2008]. In this study, patients with intermediate-risk disease, defined as clinical stage T1b to T2b tumors, PSA of at least 10 ng/ml (maximum 40 ng/ml) or a Gleason score of at least 7, were randomized to receive 70 Gy of 3D conformal radiotherapy alone or in combination with 6 months of continuous hormonal therapy given 2 months neoadjuvant, 2 months concurrent and 2 months as adjuvant therapy. After a median follow up of 7.6 years, a significant increase in the risk of all-cause mortality ($p = 0.01$) was observed in men randomized to radiation therapy compared with radiation therapy and hormonal therapy. However, the increased risk in all-cause mortality appeared to apply only to men randomized to radiation therapy with no or minimal comorbidity.

The importance of local therapy in locally advanced disease was recently addressed by Widmark and colleagues. This phase III study compared hormone therapy with and without local radiotherapy [Widmark *et al.* 2009]. Almost 900 patients were randomized to 3 months of total androgen blockade followed by continuous flutamide; or to the same

androgen ablation regimen combined with radiotherapy. The cumulative incidence at 10 years for CaP-specific mortality was 23.9% in the hormone alone group and 11.9% in the hormone plus radiotherapy group. Similarly, overall mortality was 39.4% *versus* in 29.6% in favor of the combination radiotherapy group. In addition, combined treatment reduced the high rate of PSA progression at 10 years from 74.7% to 25.9%, especially in patients with higher PSAs (>20 ng/ml). This is the first randomized study addressing the effects of local radiotherapy in locally advanced CaP. It shows that the outcome of this unfavorable disease can be importantly altered.

### Surgery and hormonal therapy

In theory, NHT, as demonstrated in the radiation literature, should improve survival of patients undergoing prostatectomy in a locally advanced setting. Putatively, the same proposed mechanisms of benefit should apply to surgical therapy, i.e. that preoperative NHT can potentially downstage locally advanced tumors, thus making them more amenable achieving negative margins at the time of surgical resection, and therefore improve patient outcomes. In 1944, Vallet first described the concept of combining systemic therapy in the form of bilateral orchiectomy with perineal prostatectomy [Vallet, 1944]. However, this combination therapy did not receive much attention until the 1980s, when reversible and less toxic forms of ADT became available. As summarized in Table 2, patients who have received NHT have shown a significant decrease in positive surgical margins and lymph node metastasis, as well as reductions in tumor size and PSA levels [Yee *et al*. 2010; Klotz *et al*. 2003; Soloway *et al*. 2002; Aus *et al*. 2002; Debruyne and Witjes, 2000; Schulman *et al*. 2000; Fair *et al*. 1999; Witjes *et al*. 1997]. However, long-term follow-up has not indicated any difference in disease-free survival as determined on the basis of PSA level or biochemical disease-free survival (BDFS).

In a more recent study by Yee and colleagues, the authors reported the outcomes of their patients who had received NHT prior to prostatectomy [Yee *et al*. 2010]. Patients with clinically localized CaP were randomized to radical prostatectomy (RP) only or 3 months of goserelin acetate and flutamide before RP. Biochemical recurrence (BCR) was defined as a detectable serum PSA level (>0.1 ng/ml) at least 6 weeks after surgery, with a confirmatory increase. The BCR-free probability at 7 years was unchanged, with 78% for patients undergoing RP only and 80% for patients undergoing NHT and RP. In addition there was no difference in the two groups with regards to local recurrence or metastasis at 8 years of follow up. Despite a longer follow up of 8 years, NHT before RP appears to be unjustified.

One proposed explanation for the failure of 3-month NHT to reduce BDFS rates is that 3 months may be an insufficient duration of NHT. It has been suggested that a longer duration of ADT may be needed to achieve an improvement in disease-free outcome in patients with organ-confined CaP. Unfortunately, long-term NHT (longer than 3 months) prior to RP in higher-risk locally advanced disease has not been investigated extensively. The Canadian Urologic Oncology Group (CUOG) performed a randomized trial of 547 men who were treated with either 3 or 8 months of NHT prior to RP [Gleave *et al*. 2001]. Of the patients who received 3 months of neoadjuvant therapy, 23% had PSMs, compared with 12% of those who received 8 months of neoadjuvant therapy. However, tumors were more often confined to the prostate in the 8-month group (80% *versus* 68%) and more often metastatic to the lymph nodes in the 3-month group (3.1% *versus* 0.4%). Despite these favorable pathologic changes, however, the overall BDFS outcome at 3 years was no different between the 3- and 8-month NHT groups.

Unlike the goal of neoadjuvant therapy to downgrade or 'shrink' the tumor, the goal of adjuvant therapy is to reduce or eliminate micrometastases, as well as any residual primary tumor after primary intervention. In addition, adjuvant hormone therapy may thereby reduce both local recurrence and distant metastases. Surprisingly, the use of adjuvant hormonal therapy following RP has been relatively understudied. Only a limited number of randomized, prospective trials have been reported. A recent meta-analysis by Shelley and colleagues revisited this topic [Shelley *et al.* 2009]. There were three studies with 4906 patients reporting adjuvant hormone therapy following prostatectomy. The only randomized trial to assess survival as an endpoint was the study conducted by the Eastern Cooperative Oncology Group (ECOG 3886) which compared hormonal therapy given immediately following RP to delayed hormonal therapy in patients with positive pelvic lymph nodes [Messing *et al.* 1999]. In this study, hormonal therapy was initiated within 12 weeks of RP in the early treatment group and at the sign of clinical evidence of

**Table 2.** Reports of prospective randomized trials on biochemical recurrence-free rates in patients treated with and without 3 months of neoadjuvant hormone therapy before radical prostatectomy [Yee *et al.* 2010; Klotz *et al.* 2003; Aus *et al.* 2002; Soloway *et al.* 2002; Debruyne and Witjes 2000; Schulman *et al.* 2000; Fair *et al.* 1999; Witjes *et al.* 1997].

| Study | Cohort size | Therapy | Duration of NHT (months) | Positive surgical margin (%) | Up to 5-year BDFS |
|---|---|---|---|---|---|
| Witjes *et al.* [1997] | 354 | RP | | 27 | 23 |
| | | Goserelin + flutamide/RP | 3 | 46 | 22 |
| Klotz *et al.* [1999] | 213 | RP | – | 64.8 | 70 |
| | | Cyproterone acetate/RP | 3 | 27.7 | 62 |
| Fair *et al.* [1999] | 148 | RP | – | 37 | 66 |
| | | Goserelin acetate + flutamide/RP | 3 | 21 | 69 |
| Schulman *et al.* [2000] | 409 | RP | – | 41.2 | 26 |
| | | Goserelin + flutamide/RP | 3 | 26.2 | 33 |
| Debruyne and Witjes [2000] | 437 | RP | – | 47.5 | 67 |
| | | Goserelin + flutamide/RP | 3 | 26.2 | 74 |
| Aus *et al.* [2002] | 126 | RP | – | 45.5 | 51.5 |
| | | Triptorelin + cyproterone/RP | 3 | 23.6 | 49.8 |
| Soloway *et al.* [2002] | 282 | RP | – | 48 | 67.6 |
| | | Leuprolide + flutamide/RP | 3 | 18 | 64.8 |
| Yee *et al.* [2010] | 148 | RP | – | 38 | 80 |
| | | Goserelin + flutamide/RP | 3 | 19 | 78 |

RP, radical prostatectomy; NHT, neoadjuvant hormone therapy; BDFS, biochemical disease-free survival.

disease progression in the deferred therapy arm. In a median follow up of 7.1 years, overall survival was better in the immediate hormonal treatment arm compared with the deferred therapy arm (seven out of 47 deaths compared with 18 of 51 in the observation arm, $p = 0.02$). This difference in overall survival was maintained when updated data with a median follow up of 11.9 years were reported in 2006 (hazard ratio [HR] 1.84, 95% confidence interval 1.01–3.35; $p = 0.04$) [Messing *et al.* 2006]. The original study has been criticized for its small sample size and for inequality of randomization between the groups. In addition, there were no guidelines for the initiation of systemic treatment in the observation arm for biochemical or symptomatic recurrence, with relatively late initiation of hormonal therapy in this group by modern standards. The study did not reach its recruitment goal of 220 patients due to the stage migration observed with the implementation of PSA-based screening, and the decreasing frequency of patients with positive lymph nodes observed during the study period. The favorable outcome in node-positive patients receiving early adjuvant hormonal therapy implies an advantage to early androgen ablation therapy in high-risk patients with minimal tumor burden. Although immediate hormonal therapy has demonstrated an improvement in overall survival in patients with gross lymph node involvement, it is not known whether such benefit will translate to those patients with localized disease.

Nontraditional hormonal therapy, in the form of antiandrogen monotherapy, has also been used in the adjuvant setting after RP. The Early Prostate Cancer Programme (EPCP) study recruited patients with T1-4M0 CaP and evaluated the efficacy of daily adjuvant bicalutamide 150 mg, which is much higher than the 50 mg dose approved in the US [McLeod *et al.* 2006]. Where specified, the radiation dose was 70 Gy given over 7 weeks. The EPCP included 4454 patients who underwent RP in three randomized, double-blind, placebo controlled trials that were prospectively designed for combined analysis. At a median follow-up interval of 7.4 years, bicalutamide significantly improved progression-free survival in the overall combined population, although an overall survival difference between treatment and placebo groups had not yet been reached. This study was a composite of three trials (trials 23, 24 and 25, powered for combined analysis). Interestingly, the North American trial (trial 23) showed no significant difference in progression. In general, patients in the North American arm of this trial had lower-risk disease. One of the important secondary findings of this study was that patients with locally advanced disease appeared to gain the most benefit from the adjuvant treatment with bicalutamide in terms of improved progression-free-survival. In fact, while survival appeared to be improved in those with locally advanced disease, survival was reduced with bicalutamide in those with localized disease,

perhaps reflecting the negative cardiovascular aspects of hormonal therapy.

In summary, no trial has been successful in producing a complete pathologic response, and no trial has demonstrated an improvement in the rate of BCR or in overall survival when using NHT prior to prostatectomy. Perhaps longer follow-up may be required to observe a survival benefit. Regardless, NHT prior to prostatectomy is not recommended and should only be administered in setting of a clinical trial or possibly for mechanical size reduction. In addition, while early adjuvant high-dose antiandrogen monotherapy may benefit those with locally advanced disease, it may not be appropriate for those with localized or low-risk cancer.

### Combined androgen blockade

The use of an oral antiandrogen with medical castration for the treatment of CaP is referred to as combined androgen blockade (CAB). In 2000, the Prostate Cancer Trialists' Collaborative Group (PCTCG) published a large meta-analysis of 27 randomized trials initiated before 1991 that compared CAB with castration alone in patients with advanced CaP [Prostate Cancer Trialists' Collaborative Group, 2000]. The results demonstrated that CAB with a NSAA (flutamide or nilutamide) reduced the risk of death by 8% compared with castration alone. However, the consensus on survival benefit was so small that CAB could not be widely recommended in clinical practice. Recently, Akaza and colleagues reported a multicenter, double-blind, controlled trial comparing CAB using the antiandrogen bicalutamide *versus* castration alone [Akaza *et al*. 2009]. At a median follow up of 5.2 years, there were fewer overall deaths with CAB than with LHRH. The 5-year overall survival rate was 75.3% for CAB *versus* 63.4% for LHRH-agonist monotherapy. Although there were more cause-specific deaths in the LHRH-agonist group, the difference was not statistically significant. PSA nadir to <0.1 ng/ml was reached in 81.4% of men on CAB and by 33.7% of men on LHRH-agonist therapy. A PSA nadir was strongly associated with overall survival. Quality of life (QoL) was assessed as a secondary endpoint in this study. Compared with LHRH-agonist monotherapy, CAB with bicalutamide did not reduce overall QoL but provided an early improvement in QoL related to lower urinary tract symptoms and pain [Arai *et al*. 2008].

### Intermittent androgen deprivation

Continuous androgen blockade has associated side effects. The well-known side effect profile of ADT includes significant QoL implications such as sexual dysfunction, hot flashes, and fatigue, and patients may develop long-term consequences such as osteoporosis, anemia, cardiovascular and metabolic disorders [Freedland *et al*. 2009; Galvão *et al*. 2009]. A multivariate analysis by Saigal and colleagues, evaluating over 22,000 men, concluded that patients receiving ADT had a 20% higher risk of cardiovascular morbidity [Saigal *et al*. 2007]. With regards to bone loss, a large, retrospective study evaluated more than 50,000 men with CaP, showing the increased of fracture in the ADT group (19.4% *versus* 12.6%). There was a significant relationship between the number of ADT doses and fracture risk [Shahinian *et al*. 2005].

The potential advantages of intermittent androgen deprivation (IAD) over continuous ADT are an improved QoL, a prolonged period of androgen dependence, a reduced incidence of the side effects normally associated with ADT, and a decrease in the cost of care. In the study by Malone and colleagues, universal loss of potency occurred during the on-treatment period but was regained by 47% of evaluable patients when therapy was withdrawn [Malone *et al*. 2005]. The strategy behind IAD, therefore, is to alternate androgen blockade with treatment cessation, allowing hormonal recovery between treatment periods. IAD is a cyclic therapy consisting of on-treatment periods followed by an observation period. The response to therapy, or occurrence of disease progression, is monitored by measuring the patient's PSA levels. The on-treatment period is generally fixed, normally lasting for 6–9 months or in some protocols until a PSA nadir of <4 ng/ml is reached.

Early survival results from phase III trials are limited and inconsistent. Mottet and colleagues reported no significant difference between patients receiving IAD and CAD with respect to median overall survival and median progression-free survival [Mottet *et al*. 2009]. Similarly, Calais da Silva and colleagues reported a time to progression that was slightly longer, although not significantly so, in the continuous ADT group than the IAD group but no significant difference in overall survival [Calais da Silva *et al*. 2009]. However, significant differences have been reported in one study. de Leval and colleagues

reported that the estimated risk of 3-year progression in CAD patients was significantly higher than in the IAD group. This difference was highlighted in patients with a Gleason score >6, where the 3-year progression rates were significantly higher in continuous ADT rather than in IAD patients [de Leval *et al.* 2002].

## Summary

Treatment of CaP is a challenge for both patients and clinicians. Hormonal therapy has traditionally been used for treatment of patients with distant metastases, since the seminal observations of Huggins and Hodges in the 1940s [Huggins and Hodges, 1941]. More recently, hormone therapy has been added to radiotherapy to improve the efficacy of treatment. The general rationales for combining external radiation therapy and hormone therapy are numerous: decreasing prostate gland volume, diminishing the number of cancer cells by inducing apoptosis and eliminating distant and regional micrometastases at the time of definitive radiotherapy. Over the last 20 years several randomized clinical trials have positive results of combined hormone therapy and localized therapy in the form of RP or radiation therapy have been performed. Although the data for the use of HT with radiation therapy in low-risk CaP is not convincing, in the group of patients with high risk of relapse (T3 or GS >7 or PSA >20 ng/ml), combined hormone therapy and radiation therapy improves treatment results and should be highly recommended. Further support of the concept of combining hormonal therapy with radiation therapy in high-risk disease has been supported by organizations such as the American Urological Association [Thompson *et al.* 2007]. The optimum duration of hormone therapy with radiation therapy will continue to be an area of research study.

Lastly, continuous hormonal therapy has been the norm for advanced disease. Concerns over the long-term effects of hormonal therapy in the older male have opened the possibility of 'hormonal holidays', technically known as intermittent hormonal therapy. A growing body of literature supports this concept with several smaller trials indicating at least equivalence with long-term hormonal therapy in terms of disease control [Abrahamsson, 2010]. The majority of studies support an improved QoL for men during the off hormonal therapy cycles. The ultimate treatment plan is an informed decision between the healthcare provider and the patient. The factors to consider in the early use of hormonal therapy are the documented and potential clinical benefits, potential toxicity and cost. It is recognized that more research is needed to guide the choice, duration, and schedule of hormonal deprivation therapy, and the impact of long-term hormone therapy with regard to toxicity and the patient's quality of life.

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