Hormonal Ablation Therapy for Metastatic Prostatic Carcinoma : A Review

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Abstract

Hormonal therapy is the standard treatment for metastatic prostatic carcinoma. The conventional surgical or medical androgen ablation therapy seems to have a similar response. Despite a higher response of CAB compared to conventional castration in metastatic disease, the controversy of survival benefit remains unsolved. Immediate treatment should be given in metastatic disease particularly in patients who have minimal metastases. In patients who have progression after CAB, antiandrogens should be withdrawn. The choices of optimal therapies for prostate cancer depend not only on the survival but also the quality of life and cost effect. Thus, the critical factors for approaching prostate cancer are appropriate patient selection and stratification. Implicit with this approach should maximize benefit from maximal androgen ablation therapy for patients who are likely to profit from it. Finally, the development of experiments, clinical trials, and novel therapeutic strategies may provide better management for prostate cancer in the future.

Key word : Metastatic Prostatic Carcinoma, Hormonal Ablation Therapy, Review

At present, prostate cancer is the most common visceral malignancy of men in western countries. In Thailand, it is the tenth malignancy among Thai men[1]. However, the incidence in Thailand seems to have increased since the prostate-specific antigen (PSA) era. Because prostate cancer does not show any symptoms in the early stage of the disease, the majority of Thai patients with prostate cancer are diagnosed with a metastatic disease. Since the studies of Huggins and Hodges in 1941[2], androgen ablation therapy has been the standard treatment for metastatic prostate cancer. Up to 80 per cent of patients with metastatic disease will respond to some form of androgen ablation. Thus, hormone management for prostate cancer continues to occupy a significant portion of the clinical practice of Thai urologists. This review will discuss the results of androgen ablation mono-

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therapy and the rationale, current results, and future development of combined androgen ablation therapy.

Androgen ablation monotherapy

A variety of methods for androgen ablation therapy can accomplish the metastatic prostatic carcinoma. The common methods used for primary androgen ablation are estrogen therapy, bilateral orchiectomy, LHRH agonist, and antiandrogens.

Estrogen therapy

Estrogen administration inhibits the release of luteinizing hormone releasing hormone (LHRH) from the hypothalamus, thereby suppressing the release of luteinzing hormone (LH) from the anterior pituitary gland and consequently decreasing testosterone from the testis[3]. It also has a direct action on leydig cell and cytotoxic effects on prostate cancer cells[4-7]. Since the 1940's, estrogens have been used for medical castration[8]. The most common drug used as estrogen therapy for prostate cancer is diethylstilbestrol (DES). The important studies of the effectiveness of DES for medical castration were performed by the Veterans Administration Cooperative Urological Research Group (VACURG)[9,10]. No difference between 5 mg/day of DES and bilateral orchiectomy was found but there was a significant risk of cardiovascular complications with 5 mg/day of DES. These cardiovascular complications were confirmed by other studies[11,12]. However, it was subsequently concluded that 1 mg/day of DES is as effective as 5 mg/day for postponing cancer progression and could reduce cardiovascular complications[9]. Recently, the European Organization for the Research and Treatment of Cancer (EORTC) Trial 30805 confirmed the efficiency of 1 mg/day of DES compared to bilateral orchiectomy[13]. Other estrogen compounds have also been used in the treatment of metastatic prostate cancer such as ethinyl estradiol, polyestradiol phosphate), estramustine phosphate, and chlorotrianisene (TACE)[14-16]. Nevertheless, all of these compounds failed to demonstrate better benefit than DES. The side effects of estrogen therapy are nausea, vomiting, gynecomastia and serious cardiovascular complications. The lethal cardiovascular complications are myocardial infarction, congestive heart failure, deep vein thrombophlebitis, and pulmonary embolism[17,18]. It has been purposed that a low dose of aspirin daily may minimize the cardiovascular complications. Unfortunately, there is no study to support this use of aspirin in decreasing these complications[19,20]. Nevertheless, parenteral estrogen may not have the risk of cardiovascular death that is described in oral estrogen[4]. In conclusion, estrogen therapy is as effective as other standard monothrapy treatment; bilateral orchiectomy or LHRH agonist[4,21]. However, because of serious cardiovascular complications, estrogen therapy is not a treatment option in many patients and not available in many countries. At present, estrogen therapy is rarely used in Thailand.

Bilateral orchiectomy

Bilateral orchiectomy reduces circulating testosterone to castration levels approximately 3 to 12 hours after surgery with the mean time of 8.6 hours[22]. Subjective or objective response rate is up to 80 per cent of patients[9]. Median survivals of metastatic disease treated with bilateral orchiectomy therapy range from 18 to 27 months[23-25]. Rarely, bilateral orchiectomy is useful for immediate androgen suppression in patients with extensive metastatic diseases complicated by such life threatening conditions as spinal cord compression or bilateral ureteral obstruction[19]. The advantages are cost and being well tolerated. The disadvantages are decreased libido, impotence, weight gain, psychological effects, and hot flushes. The most important disadvantage is its irreversibility. To allay some of the psychological effects of an empty scrotum, subcapsular orchiectomy is as effective as a simple orchiectomy[26]. At present, bilateral orchiectomy remains the gold standard for ablation of testiscular androgen. Despite decreasing in Western countries, it is still recommended in some men to avoid a higher cost, inconvenience of frequent depot injections of luteinizing hormone releasing hormone (LHRH) agonists, and cardiovascular side effects of diethylstilbestrol (DES). In Thailand, including Siriraj Hospital, this method has been utilized as a standard treatment for metastatic prostatic carcinoma[1].

LHRH Agonists

In 1971, the LHRH hormone was isolated. LHRH effects luteinizing hormone (LH) and follicle stimulating hormone (FSH) in the pituitary gland[27]. Interestingly, continuous administration of LHRH paradoxically affects the pituitary gland leading to suppression of LH and FSH secretion,

followed by a blockade of testosterone and atrophy of both prostate gland and seminal vesicle[28]. Furthermore, experimental data suggested that LHRH agonists have a direct effect of inhibition on prostate cancer cell line[29]. Currently, LHRH agonists have become widely available as medical castration to treat metastatic disease[30]. LHRH agonists were found as effective as estrogen therapy and bilateral orchiectomy in terms of response rates and survival but superior in terms of physical and psychological effects, respectively[23,26,30-32]. The advantages of LHRH agonist therapy are tolerance and reversible androgen ablation. The disadvantages are an expensive method, hot flushes, a flare phenomenon, loss of libido, and impotence. Importantly, the initial administration of LHRH agonist causes a stimulation of LH and FSH release and subsequently increases testosterone from the testis before these hormones are shut down. Flare phenomenon may increase pain and cause serious effects such as paralysis from pathological fracture or bilateral ureteral obstruction[33]. Fortunately, it was found that an initial administration of antiandrogens such as flutamide, nilutamide, and cyprosterone acetate (CPA) was effectively utilized for prevention of flare effects[34-36]. Thus, combination therapy with an antiandrogen initially is recommended to prevent such side effects.

Recently, LHRH antagonist, a new form of LHRH related androgen ablation, has been investigated. Experimental data were conducted with using LHRH antagonists which directly block the LHRH receptor. This resulted in immediate suppression of androgen production[37]. Unfortunately, early use of the LHRH antagonist was associated with anaphylactoid reaction, histamine releasing, necessity of using acidic formulation for delivery, or relative water insolubility[19]. However, some newer compounds have averted some of these local injection problems.

Antiandrogens

Testosterone is transformed into dihydrotestosterone (DHT) by 5α-reductase enzyme in prostatic tissue. DHT, a stronger potent androgen, interacts with androgen receptor. The androgen-receptor complex stimulates expression of genes mediating androgen specific functions resulting in cell growth[28]. Antiandrogens are purposed to inhibit the interaction between androgen and receptor. They are classified into two major categories; steroidal antiandrogen compounds and nonsteroidal antiandrogen compounds.

Steroidal antiandrogen compounds inhibit androgen action at the androgenic receptor level. They also have progestational effects. Steroidal antiandrogen suppresses LHRH, LH and consequently decreases testosterone from the testis[38]. These compounds utilized in the treatment of prostate cancer are cyproterone acetate (CPA), megestrol acetate, and medoxy-progesterone acetate (MPA). Megestrol acetate is often used in hormonal refractory disease. The important steroidal antiandrogen compound is CPA, which is also available in Thailand. It has been widely used in European countries, but not in the United States, for treatment of metastasis prostate cancer since 1966[41]. Jacobi et al showed that CPA achieved similar survival to bilateral orchiectomy[42]. The European Organization for Research and Treatment of Cancer (EORCT) 30761 demonstrated that there was no significant difference in survival between CPA and DES, whereas, medoxy-progesterone acetate showed inferior results[43]. However, a significant difference in median time to progression between CPA alone and LHRH agonists in favor of the latter were demonstrated by other studies[44]. Some investigators observed that CPA could not maintain a prolonged castration effect and needed a low dose of DES for maintaining castration levels of testosterone[45]. Therefore, monotherapy with CPA appears not to be more effective than the standard bilateral orchiectomy or estrogen therapy. The side effects of CPA were impotence and loss of libido in 86 per cent of patients[42]. The advantage is that it does not cause the hot flushes which occur after medical castration with LHRH agonists alone or bilateral orchiectomy. CPA was also described for antiflare effect at dose 100 mg/day for 3 weeks before initiation of LHRH agonists[46].

Nonsteroidal antiandrogen compounds are pure antiandrogens because of inhibition at the androgenic receptor level only. This blockade results in the increase of LH and testosterone in the serum. Thus, it consequently preserves libido and potency in approximately 80 per cent of the patients[47-49]. The common side effects are gynecomastia and breast tenderness because of the high level of estrogen that aromatizes from testosterone. Currently, there are three antiandrogen compounds for treatment of prostate cancer; flutamide, nilutamide, and bicalutamide. However, nilutamide and bicalutamide are not yet available in Thailand.

Flutamide was first described by Neri in 1972[50]. Many studies reported subjective and objective response rates among 50-90 per cent using flutamide as a monotherapy[47,51-53]. Boccon-Gibod reported that their randomized phase III study of 104 newly diagnosed metastatic disease patients receiving flutamide 750 mg/day or bilateral orchiectomy showed no difference in progression free survival between two arms[54]. Lund and Rasmussen demonstrated that there was no significant difference between flutamide 750 mg/ day and 3 mg/ day of DES[48]. In contrast, Chang et al indicated that there was a 17 month difference in survival comparing 750 mg/day of flutamide to 3 mg/ day of DES[55]. Flutamide has also been used in various modalities such as combined androgen ablation, a secondary line in hormonal refractory disease, and an antiflare effect by a 2 week pretreatment of flutamide administration[35]. The side effects of flutamide are nausea, vomiting, diarrhea, breast tenderness, gynecomastia, and hepatic toxicity[56].

Nilutamide differs from flutamide only in its lateral chain. This change prolongs its half life up to 40 hours. Thus, it was recommended as one daily dosage of 300 mg[57]. Only one published study for nilutamide monotherapy[58] showed that the mean progression free survival and over all survival were 9 and 23 months, respectively. The side effects are alcohol intolerance, nausea, liver toxicity, interstitial lung disease, and diminished visual adaption to darkness[59]. However, nilutamide is more widely used with LHRH agonists for combined androgen ablation.

Bicalutamide is the novel of the pure antiandrogens with a long half life[60]. Its safety appears very good; without significant pulmonary, gastrointestinal, or visual side effects. The objective and subjective responses of bicalutamide monotherapy were approximately 50-55 per cent in metastatic disease[58,61,62]. In comparative studies, 2 of 3 randomized phase III studies by Iversen et al reported that 50 mg of bicalutamide was inferior to either surgical or medical castration in terms of time to treatment failure, time to progression including overall survival from these 3 studies[61]. These results were confirmed by Chodak[63,64]. However, other randomized studies that compared 50 mg of bicalutamide and castration showed no difference in time to progression[65]. Bicalutamide has also been used for combined androgen ablation.

Other monotherapies

Besides the basic methods of hormonal therapy, as stated above, other androgen ablation methods have been used such as estramustine, ketoconazole, aminoglutethamide, or corticosteroid. Ketoconazole is an antifungal drug that inhibits a cytochrome p-450 dependent step for synthesis both testiscular and adrenal androgens[66]. Aminoglutethamide, like ketoconazole, acts at a cytochrome p-450 and causes a decrease of dehydroepiandrosterone sulfate (DHEAS), androsternedione and testosterone level[67]. Corticosterone is purposed to suppress adrenal androgen. These drugs are generally used as a secondary hormonal treatment in hormonal refractory prostate cancer. The results of these therapies are varied. Thus, caution should be taken for interpretation.

Combined Androgen Ablation (CAB) Therapy

Even though conventional surgical or medical primary androgen ablation monotherapy is effective in suppression of testicular androgen in many prostate cancer patients, their diseases continue to progress. Importantly, it is possible that adrenal androgen that remains in the circulation stimulates tumor cell growth. Theoretically, prostate cancer is composed of different clones of cells with varying degrees of androgen sensitivity or androgen resistance. Although conventional surgical or medical castration alters the clones that require large amounts of dihydrotestosterone (DHT), it fails to significantly alter the other clones that require a low concentration of DHT[68]. Furthermore, many experiments have supported the role of adrenal androgens in stimulating prostate tumor cell growth. Harper et al demonstrated that there was radiolabelled DHT in patients undergoing prostatectomy for benign prostatic hyperplasia (BPH) after those isotopes were labelled with androstenedione or dehydroepiandrosterone (DEHA) for half an hour before surgery[69]. This supports the conversion of their adrenal precursors to DHT. Despite serum testosterone at castration levels, intracellular DHT persisted in high levels in patients who received androgen ablation monotherapy[70-72]. In addition, other studies showed a significant reduction of prostatic DHT when utilizing ketoconazole for blocking adrenal androgen with conventional monotherapy castration[73]. Thus, persistent DHT in prostatic tissue results from conversion of inactive adrenal

androgen precursors; dehydroepiandrosterone (DEHA), its sulfate (DEHAS), and androstenedione into testosterone and subsequent DHT[28,74]. Labrie estimated that approximately 40 per cent of prostatic DHT originates from adrenal precursors [28]. Thus, the concept of necessity to eliminate all sources of androgen provides the basis for combined androgen ablation. This concept is not new. In 1945, Huggins and Scott performed bilateral adrenalectomy as secondary hormonal therapy in patients whose diseases progressed following bilateral orchiectomy[75]. Unfortunately, because of a high mortality, that procedure was abandoned. Since the discovery of an antiandrogen that inhibits androgenic action at the androgen receptor level in the target cell, combined androgen ablation: eliminate testiscular androgen by surgical or medical castration plus antiandrogens, was firstly advocated by Labrie et al[76]. They reported a 97 per cent objective response rate compared to 60-70 per cent in previous castration or estrogen therapy in metastatic prostatic carcinoma.

Currently, the definition of metastatic disease has changed considerably[77]. The new definition is D1 for pelvic lymph node metastases; D1.5 for rising PSA after failed local therapy; D2 for metastatic disease in bone and/or other organs; D2.5 for rising PSA after nadir level; D3 for hormone refractory prostate cancer; D3S for hormonally sensitive; and D3I for hormonally insensitive. According to this concept, hormonal therapy has been an important method to treat metastasis. To improve response rates, time to progression, and survival, CAB strategy has been utilized. Recently, CAB has been widely investigated and compared to conventional castration monotherapy. The outcomes of three well designed randomized studies that support the survival benefit of CAB are shown in Table 1. The large confirmatory trial conducted by the South West Oncology Group (SWOG-INT 0036) was reported by Crawford et al[78]. This randomized 603 patients study compared leuprolide plus 750 mg/day of flutamide with leuprolide plus placebo in metastatic disease. With up to 48 months of follow-up, a 18.7 per cent increase in median time to progression (16.5 months *versus* 13.9 months) and a 25.8 per cent increase in median time of overall survival (35.6 months *versus* 28.3 months) were demonstrated in CAB arm with statistical significance. The European Organization for Research and Treatment of Cancer (EORTC) 30853 study by Denis et al compared goserelin acetate plus 750 mg/day of flutamide with bilateral orchiectomy in 310 patients [25]. With a median time follow-up of 5 years, 25 week increase of time to progression (71 weeks *versus* 46 weeks) and 7 month increase of overall survival (34.4 months *versus* 27.1 months) were noted in goserelin plus flutamide arm with statistical significance. The Anandron Study Group by Janknegt et al compared bilateral orchiectomy plus 300 mg/day of nilutamide with bilateral orchiectomy alone in 457 patients[24,79]. With up to 8.5

Table 1. Clinical studies that support the survival benefit of CAB.

Clinical trial	Therapy	No.	Follow-up	Response rate	Time to progression	Survival
NCI INT 0036, Crawford et al (78)	leupro	300	48 mos (max)	36.1%	13.9 mos	28.3 mos
	leupro+flut	303		42.8%	16.5 mos p=0.039	35.6 mos p=0.035
EORTC-30853, Denis et al (25)	orch	155	5 yrs (median)	59%	46 wks	27.1 mos
	goserelin+flut	155		58% (obj)	71 wks p=0.002	34.4 mos p=0.02
Anadron-Group Janknegt et al (24,79)	orch	232	8.5 yrs (max)	24%	14.7 mos	29.8 mos
	orch+nilut	225		41% (obj)	21.2 mos p=0.002	37 mos p=0.013

NCI: National Cancer Institute, INT: Intergroup, EORTC: European Organization for the Research and Treatment of Cancer, orch: orchiectomy, leupro: leuprolide acetate, flut: flutamide, nilut: nilutamide, wk: week, mo: month, yr: year, obj: objective, max: maximum.

years of follow-up, significant benefits were achieved of 7 month prolongation in CAB arm in both time to progression (21.2 months *versus* 14.7 months) and survival (37 months *versus* 29.8 months. Interestingly, minimal metastatic diseases [80], an absence of metastasis in skull, rib, long bone, or soft tissue other than lymph node, were also evaluated. In the two studies; INT 0036 and EORTC 30853, these significant benefits of CAB are more apparent in patients with minimal metastatic disease and good performance. The median survival time was 61 months in CAB arm *versus* 41 months in monotherapy arm in INT 0036 study[78].

Nevertheless, the validity of CAB is still controversial. Many randomized studies that do not support the survival advantage of CAB are shown in Table 2. Beland et al conducted a trial comparing bilateral orchiectomy alone with bilateral orchiectomy plus 300 mg/day of nilutamide in 204 patients [23]. No significant difference in terms of time to

Table 2. Clinical studies that do not support the survival benefit of CAB.

Clinical trial	Therapy	No.	Follow-up	Response rate	Time to progression	Survival
Crawford et al (NCI INT 0105) (21)	orch orch+flut	681 690	5 yrs (max)	61% 81% (by PSA)	18 mos 21 mos NS	30 mos 31 mos NS
Iversen et al (Danish Prostate Cancer Gr) (82)	orch goserelin+flut	133 129	57 mos (median)		16.8 mos 16.5 mos NS	27.6 mos 22.7 mos NS
Beland et al (23)	orch orch+nilut	103 105	48 mos (max)	61% 78% p=0.013	11.7 mos 12.4 mos NS	18.9 mos 24.3 mos NS
Bertagna et al (81)	orch orch+nilut	506 550		33% 50% p<0.001	Odds ↓ in CAB p=0.05	Odds ↓ in CAB NS
Tyrell et al (83)	goserelin goserelin+flut	151 150	56.2 mos (median)		NS	26.9 mos 29.0 mos NS
Boccardo et al (PONCAP) (both C&D) (84)	goserelin goserelin+flut	373 all	24 mos (median)		12 mos 12 mos NS (D only)	32 mos 34 mos NS (C&D)
Ferrari et al (85)	buserelin buserelin+flut	46 50	88 wks 86 wks (median)		22 wks 32 wks NS	
Klijn et al (EORTC-30843) (86)	orch buserelin+CPA buserelin+(2-wks of CPA)	48 36 52	189 wks (median)	54% 47% 45%	NS	NS
Robinson et al (87)	orch orch+CPA DES	110 117 107	48 mos (median)		NS	NS

NCI: National Cancer Institute, INT: Intergroup, EORTC: European Organization for the Research and Treatment of Cancer, PONCAP: Italian Prostatic Cancer Project, CAB: combined androgen ablation, orch: orchiectomy, flut: flutamide, nilut: nilutamide, DES: diethylstibestrol, CPA: cyproterone acetate, wk: week, mo: month, yr: year, NS: no significance, max: maximum.

progression and overall survival was addressed. The study of Bertagna et al confirmed the previous study that the combination of orchiectomy with nilutamide did not significantly improve the survival advantage[81]. The Danish Prostate Cancer Group studied 262 patients and failed to demonstrate the superiority of goserelin plus flutamide compared with bilateral orchiectomy in terms of time to progression (16.5 months *versus* 16.8 months) and survival (22.7 months *versus* 27.6 months) in metastatic disease. But the significant advantages of CAB in terms of time to progression and survival appeared in the minimal metastatic disease subgroup were addressed in this study[82]. Tyrrell et al studied goserelin acetate alone compared to goserelin acetate plus flutamide. No significant difference was found between the two arms in survival (29 months versus 26.9 months) with median time follow-up of 56.2 months[83]. The Italian Prostatic Cancer Project (PONCAP) Study Group also compared goserelin plus 750 mg/day of flutamide and goserelin acetate alone in both stage C and D of 373 patients[84]. With median time follow-up of 24 months, no significant difference was found between the two arms in both time to progression and survival. Ferrari et al reported the same results between buserelin plus flutamide and buserelin alone in 96 patients[85]. The EORTC 30843 Genitourinary Group conducted a three arm randomized study of buserelin plus two weeks of CPA, buserelin plus continuous addition of CPA, and bilateral orchiectomy alone[86]. No significant difference among the three groups in terms of response rate, time to progression, and overall survival was found. Robinson et al also reported three arms of 1 mg/day of DES, bilateral orchiectomy, and bilateral orchiectomy plus CPA [87]. Again, this study failed to indicate the superiority of CAB. However, there are some conflicting opinions that an insufficient statistical power may be due to an insufficient number of patients or too early to consider the significant difference. The good examples for these opinions are the EORTC 30853 and the Anandron Study Group studies. Primary analysis showed no significance of survival benefit but the longer follow-up showed a statistical significance[24,25,79,88]. The result of a recent large randomized study (NCI-INT 0105) comparing bilateral orchiectomy alone and bilateral orchiectomy plus 750 mg/day of flutamide was reported by Crawford et al[21]. This study failed to achieve the benefit of the addition of flutamide to bilateral orchiectomy in terms of time to progression (18 *versus* 21 months, respectively) and survival (30 *versus* 31 months, respectively) in metastatic disease. In patients with minimal good risk disease, it also failed to demonstrate an advantage. The Prostate Cancer Trialists' Collaborative Group reported a large meta-analysis of CAB outcome[89]. This study reviewed 22 randomized trials and total of 5710 patients with advanced prostate cancer. They compared conventional castration (surgical or LHRH agonists) *versus* CAB (conventional castration plus antiandrogens such as flutamide, nilutamide, and cyproterone acetate). With a median follow-up of 40 months, 57 per cent of the patients died. The overall mortality among patients with castration alone was 58.4 per cent compared to 56.3 per cent among those with CAB. Five year survivals were 22.8 per cent and 26.2 per cent respectively without significant improvement of 3.5 per cent (95% CI 0-7%). No significant benefit of time to death in addition to CAB appeared. Although this study concluded that CAB does not result in a longer survival than conventional castration in metastatic diseases, it partially supported the benefit of CAB in minimal metastatic diseases. However, there are some arguments against this conclusion. The three antiandrogens used have different endocrinological effects and may not be comparable treatment. It is probably too early to show the statistical significance of cancer mortality because of short median time of follow-up[90]. Also 5 year survival points may not be appropriate in a disease where the median survival is only 3 years. Other parameters than time to progression and survival are observed. Although many studies do not support the survival benefit, most of those studies confirmed the benefits in terms of subjective and objective responses such as bone pain and levels of tumor marker [23,21,81].

At present, the controversy of an advantage of CAB as a first line therapy for newly diagnosed metastatic disease remains unclear. Even though some studies fail to demonstrate statistical power in term of survival, most show a benefit of CAB in terms of subjective or objective response rates. Furthermore, the survival benefit was definitely demonstrated in several studies particularly in minimal diseases.

Timing for androgen ablation therapy

Since androgen ablation therapy has become the standard treatment for metastatic

disease, treatment results in a temporary response. The relapse or progression to androgen independent stage (hormonal refractory disease) usually occurs within two years. For this reason, the optimal timing; immediate *versus* deferred, for hormonal therapy is widely debated. It is generally agreed that symptomatic metastatic disease should be promptly treated by hormonal therapy. The controversy of immediate versus deferred treatment remains for asymptomatic patients. In 1973, Byar suggested deferring androgen ablation until symptoms occurred because survival is not prolonged by early androgen ablation[91]. In contrast, the later report demonstrated an advantage in delaying progression and survival on early androgen ablation[9]. Crawford et al also showed benefit in men with good performance and minimal metastatic disease treated with CAB therapy at the time of diagnosis[78,92]. These results suggested that the best outcomes are seen in patients treated early in the course of their diseases. Many retrospective studies have shown that progression is prolonged by early hormonal treatment in surgically proven stage D1 patients. The results from EORTC 30846 also suggested the superiority of an immediate treatment approach[93]. A significant benefit in delaying progression of immediate treatment (100 months versus 43 months in the deferred group) in patients with stage D1 was demonstrated by Kramolowski[94]. Zagars et al and van den Ouden et al also showed similar results in stage N+ M0 patients [95,96]. Unfortunately, these studies were not a randomized study for the purpose of resolving the controversy of immediate *versus* deferred treatment. Subsequently, the Medical Research Council (MRC) conducted the first randomized study of this issue in 1997[97]. This large study of 938 patients with locally advanced or asymptomatic metastatic disease randomized immediate androgen ablation treatment (orchiectomy or LHRH agonists) *versus* deferred treatment until symptoms occurred. They demonstrated significant advantages in prolongation of progression and development of pain. Furthermore, complications from advanced metastatic disease were approximately twice as common as in the deferred group. Importantly, they showed a significantly longer overall survival in the immediate group particularly in patients with stage M0.

In conclusion, most studies suggest that immediate androgen ablation therapy could delay the progression of metastatic patients particularly in minimal diseases. Furthermore, it improves quality of life and prevents complications from advanced metastasis such as paralysis from spinal cord compression, bladder outlet obstruction, or uremia. Finally, prolongation of death is addressed in one randomized study[97].

Antiandrogen Withdrawal Syndrome

Since CAB therapy is widely considered, the use of antiandrogens has been increased. Scher and Kelly reported the paradoxical response on withdrawal of flutamide in approximately 40 per cent of patients with progression on LHRH agonist plus flutamide treatment[98]. It was also reported by Dupont et al[99]. A decrease of PSA, symptoms, and objective signs has been reported. Recently, bicalutamide, DES, steroidal antinadrogen, and megestrol acetate have also been reported[100-103]. Many investigators hypothesized the mechanism that androgen receptor probably mutates and recognizes the antiandrogen as a stimulator. Veldscholte et al demonstrated this hypothesis in the prostate cancer cell line[104]. At present, the recommendation for management in patients who progress after CAB therapy is withdrawal of antiandrogens.

Intermittent androgen ablation therapy

To improve quality of life, reduce side effects and cost of treatment, and delay time to development of hormone resistance and tumor progression, a novel strategy, intermittent androgen ablation therapy, is being investigated. The hypothesis is that progression is associated with adaptation of cancer cells to independent stage by initiation of androgen ablation[105]. Thus, replacing androgen before the initiation of progression will cause the surviving stem cell to give rise to an androgen dependent cell for retreatment by androgen ablation. It was first described by Klotz et al[106]. Androgen ablation continues until the PSA level reaches its nadir and is continued for a set period of time. It is then stopped until the PSA starts to increase again to a certain level. Laboratory data have shown that the time to hormone independent cancer may be extended by using this new approach[107]. Goldenberg et al[108] studied 47 patients with two cycles of intermittent CAB therapy. After stopping treatment, serum testosterone levels returned to normal range within 8 weeks. However, the mean and median time to progression were similar to the expected results of continuous androgen ablation.

Importantly, in the non-treatment period, libido and potency returned in patients who reported normal sexual function before therapy. However, further randomized study should be conducted to indicate whether intermittent hormonal therapy alters survival.

Future Direction

Hormonal therapy for prostate cancer is changing dramatically. Despite improving the subjective and objective responses, the delaying of time to progression and survival of CAB in metastatic prostate cancer, progression to androgen independent stage occurs in most patients. The hypothesis for this phenomenon is an adaptation and a clonal selection modal(109). Androgen-independent state of cells surviving on androgen ablation therapy may result from the ability of a small number of initially androgen-dependent stem cells to adapt to an altered hormone environment(98). This phenomenon appears to occur at a molecular level and seems to occur despite a clinically evident response. Many experimental data support that during the active cell death process by androgen ablation, a number of novel RNAs and proteins are induced (98,110,111). A variety of genes such as P53 and BLC2 has been implicated in prevention of the apoptosis. P53 is induced following androgen ablation and inhibits the apoptotic pathway(112,113). BCL2 gene also interferes with apoptosis and is correlated with the progression of prostate cancer from androgen dependence to androgen independence(114). Investigators recently found that androgen receptor (AR) gene mutations could result in diminished ligand specificity of androgen receptors and are the molecular cause of androgen insensitivity syndrome(115). Amplification of the androgen receptor (AR) gene is another novel molecular mechanism that may explain why cancer cells become resistant to androgen ablation therapy. It increases the expression of the AR gene, which enables the cancer cells more effectively to utilize the residual low levels of androgens for sustaining cell growth(116). From the experimental data, it was purposed that the discovery of a new molecular mechanism of androgen ablation therapy resistance should be proved for development of more effective hormonal therapy regimens as well as other innovative strategies for inducing active cell death and eradication of stem cells. In addition, immunomodulatory drugs, monoclonal antibody techniques, or genetically engineered programmed cancer cell death (apoptosis) should be available to eradicate tumors in the future.

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REFERENCES

1. Soontrapa S, Tantiwong A, Panawattanakul S, et al. Prostatatic carcinoma at Siriraj Hospital. Siriraj Hosp Gaz 1997; 49: 107-13.
2. Huggins C, Hodes CV. Studies of prostatic cancer. 1. The effects of castrations, of estrogen and of androgen injections on serum phosphatases in metastatic carcinoma of prostate. Cancer Res 1941; 1: 293-307.
3. Bruchorsky N. Androgen and antiandrogens. In Holland JF, Frei EIII, Bast RC, et al (eds) : Cancer Medicine, 3rd. Philadelphia, Lea and Febiger, 1993: 884-96.
4. Cox RL, Crawford ED. Estrogens in the treatment of prostate cancer. J Urol 1995; 154: 1991-8.
5. Schulz P, Bauer HW, Brade WP, Keller A, Fittler F. Evaluation of the cytotoxic activity of diethylstilbestrol and its mono and diphosphate towards prostatic carcinoma cells. Cancer Res 1988; 48: 2867-70.
6. Schulz P, Link TA, Chaudhuri L, Fittler F. Role of the mitochondrial bcl-complex in the cytotoxic action of diethylstilbestrol-diphosphate toward prostatic carcinoma cells. Cancer Res 1990; 50: 5008-12.
7. Robertson CN, Roberson KM, Padilla GM, et al. Induction of apoptosis by diethylstilbestrol in hormone-insensitive prostate cancer cells. J Nat Cancer Inst 1996; 88: 908-17.
8. Herbst ?.P. Effects of estradiol dipropionate and diethylstilbestrol on malignant prostatic tissue. Trans Amer Assn Genitourin Surg 1941; 34: 195.
9. Byar DP, Corle DK. Hormone therapy for prostate cancer: results of the Veterans Administration Cooperative Urological Research Group studies. Nation Cancer Inst Monogr 1988; 7: 165-70.
10. Veterans' Administative Co-operative Urological Research Group: Treatment and survival of patients

with cancer of the prostate. Surg Gynecol Obstet 1967; 124: 1011-7.
11. de Voogt HJ, Smith PH, Pavone-Macaluso M, de Pauw M, Suciu S. Cardiovascular side effects of diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate and estramustine phosphate used for the treatment of advanced prostatic cancer: results from European Organization for Research on Treatment of Cancer trials 30761 and 30762. J Urol 1986; 135: 303-7.
12. Henriksson P, Edhag O. Orchidectomy versus oestrogen for prostatic cancer: cardiovascular effects. Br Med J 1986; 293: 413-5.
13. Robinson MR. A further analysis of European Organization for Research and Treatment of Cancer protocol 30805. Orchidectomy versus orchidectomy plus cyproterone acetate versus low-dose diethylstilbestrol. Cancer 1993; 72: 3855-7.
14. Morales A, Pujari B. The choice of estrogen preparations in the treatment of prostatic cancer. CMAJ 1975; 113: 865-7.
15. Bishop MC, Lemberger RJ, Selby C, Lawrence WT. Oestrogen dosage in prostatic cancer: the threshold effect?. Br J Urol 1989; 64: 290-6.
16. Bishop MC, Selby C, Taylor M. Plasma hormone levels in patients with prostatic carcinoma treated with diethylstilboestrol and estramustine. Br J Urol 1985; 57: 542-7.
17. Peeling WB. Phase III studies to compare goserelin (Zoladex) with orchiectomy and with diethylstilbestrol in treatment of prostatic carcinoma. Urology 1989; 33(suppl): 45-52.
18. Lukkarinen O, Kontturi M. Comparison of a long-acting LHRH agonist and polyoestradiol phosphate in the treatment of advanced prostatic carcinoma. An open prospective, randomized multicentre study. Scand J Urol Nephrol 1994; 28: 171-8.
19. Garnick MB. Hormonal therapy in the management of prostate cancer: from Huggins to the present. Urology 1997; 49(Suppl 3A): 5-15.
20. Smith PH. Esrogens reconsidered. Semin Surg Oncol 1995; 11: 72-5.
21. Crawford ED, Eisenberger MA, McLeod DG, Wilding G, Blumenstein BA. Comparison of bilateral orchiectomy with or without flutamide for the treatment of patients with stage D2 adenocarcinoma of the prostate. Results of NCI intergroup study 0105 (SWOG and ECOG). J Urol 1997; 157: 336, Abs#1311.
22. Lin BJ, Chen KK, Chen MT, Chang LS. The time for serum testosterone to reach castrate level after bilateral orchiectomy or oral estrogen in the management of metastasis prostate cancer. Urology 1994; 43: 834-7.
23. Beland G, Elhilali M, Fradet Y, et al. Total androgen ablation: Canadian experience. Urol Clin North Am 1991; 18: 75-82.
24. Janknegt RA, Abbou CC, Bartoletti R, et al. Orchiectomy and nilutamide or placebo as treatment of metastatic prostatic cancer in a multinational double-blind randomized trial. J Urol 1993; 149: 77-83.
25. Denis LJ, Carnelro de Moura JL, Bono A, et al. Goserelin acetate and flutamide versus bilateral orchiectomy: a phase III EORTC trial (30853). EORTC GU Group and EORTC Data Center. Urology 1993; 42: 119-30.
26. Zhang XZ, Donovan MP, Williams BT, Mohler JL. Comparison of subcapsular and total orchiectomy for treatment of metastatic prostate cancer. Urology 1996; 47: 402-4.
27. Schally AV, Arimura A, Baba Y, et al. Isolation and properties of the FSH and LH-releasing hormone. Biochem Biophys Res Commun 1971; 43: 393-9.
28. Labrie F, Belanger A, Simard J, Labrie C, Dupont A. Combination therapy for prostate cancer. Endocrine and biologic basis of its choice as new standard first-line therapy. Cancer 1993; 71: 1059-67.
29. Stenner J, Rosenblum M, Miller GJ, Crawford ED. Orchiectomy with or without flutamide: Is there still a place for combined androgen blockade in the therapy of advance prostate cancer? Urology Int 1997 (in press).
30. Leuprolide Study Group. Leuprolide versus diethyl-stilbestrol for metastatic prostate cancer. N Engl J Med 1984; 311: 1281-6.
31. Klioze SS, Miller MF, Spiro TP. A randomized, comparative study of buserelin with DES/orchiectomy in the treatment of stage D2 prostatic cancer patients. Am J Clin Oncol 1988; 2(suppl): 5176-82.
32. Koutsilieris M, Faure N, Tolis G, Laroche B, Robert G, Ackman CF. Objective response and disease outcome in 59 patients with stage D2 prostatic cancer treated with either Buserelin or orchiectomy. Disease aggressivity and its association with response and outcome. Urology 1986; 27: 221-8.
33. Schroeder FH, Lock TM, Chadha DR, et al. Metastatic cancer of the prostate managed with buserelin versus buserelin plus cyproterone acetate. J Urol 1987; 137: 912-8.
34. Isurugi K, Fukutani K, Ishida H, Hosoi Y. Endocrine effects of cyproterone acetate in patients with prostatic cancer. J Urol 1980; 123: 180-3.
35. Labrie F, Dupont A, Belanger A, Lachance R. Flutamide eliminates the risk of disease flare in prostatic cancer patients treated with a luteinizing hormone-releasing hormone agonist. J Urol 1987; 138: 804-6.
36. Kuhn JM, Billebaud T, Navratil H, et al. Prevention of the transient adverse effects of a gonadotropin-releasing hormone agonist (buserelin) in metastatic prostatic carcinoma by administration of an

antiandrogen (nilutamide). N Engl J Med 1989; 321: 413-8.
37. Pinski J, Yano T, Miller G, Schally AV. Blockade of the LH response induced by the agonist D-Trp-6-LHRH in rats by a highly potent LH-RH antagonist SB-75. Prostate 1992; 20: 213-24.
38. Schroder FH. Cyproterone acetate mechanism of action and clinical effectiveness in prostate cancer treatment. Cancer 1993; 72: 3810-5.
39. Vener PM, Klotz PG, Kotz LH, et al. Megestrol acetate plus minidose diethylstibestrol in the treatment of carcinoma of prostate. Semin Oncol 1988; 15 (2 suppl1) : 62-7.
40. Patel SR, Kvols LK, Hahn RG, Windschilt LH, Levitt R, Therneau T. A phase II randomized trial of megestrol acetate or dexamethazone in the treatment of hormonally refractory advance carcinoma of the prostate. Cancer 1990; 66: 655-68.
41. Scott WW, Schirmer HK. A new oral progestational steroidal effective in treating prostatic cancer. Trans Am Assoc Genito-Urn Surg 1966; 58: 54-62.
42. Jacobi GH, Altwein JE, Kurth KH, Basting R, Hohenfellner R. Treatment of advanced prostatic cancer with parenteral cyproterone acetate: a phase III randomised trial. Br J Urol 1980; 52: 208-15.
43. Pavone-Macaluso M, de Voogt HJ, Viggiano G, et al. Comparison of diethylstilbestrol, cyproterone acetate and medroxyprogesterone acetate in the treatment of advanced prostatic cancer: final analysis of a randomized phase III trial of the European Organization for Research on Treatment of Cancer Urological Group. J Urol 1986; 136: 624-31.
44. Thorpe SC, Azmatullah S, Fellows GJ, Gingell JC, O'Boyle PJ. A prospective, randomised study to compare goserelin acetate (Zoladex) versus cyproterone acetate (Cyprostat) versus a combination of the two in the treatment of metastatic prostatic carcinoma. Eur Urol 1996; 29: 47-54.
45. Goldenberg SL, Brushovsky NB. Use of cyproterone acetate in prostate cancer. Urol Clin North Am 1991; 18: 111-22.
46. Hugosson J, Abrahamsson PA, Ahlgren G, et al. The risk of malignancy in the surgical margin at radical prostatectomy reduced almost three-fold in patients given neo-adjuvant hormone treatment. Eur Urol 1996; 29: 413-9.
47. Sogani PC, Vagaiwala MR, Whitmore WF Jr. Experience with flutamide in patients with advanced prostatic cancer without prior endocrine therapy. Cancer 1984; 54: 744-50.
48. Lund F, Rasmussen F. Flutamide versus stilbestrol in the management of advanced prostatic cancer, a controlled prospective study. Br J Urol 1988; 61: 140-2.
49. Migliari R, Muscas G, Usai E. Effect of Casodex on sleep-related erections in patients with advanced prostate cancer. J Urol 1992; 148: 338-41.
50. Neri R, Florance K, Koziol P, Van Cleave S. A biological profile of a nonsteroidal antiandrogen, SCH (4'-nitro-3'trifluoromethylisobutyranilide). Endocrinol 1972; 91: 427-37.
51. Delaere KP, Van Thillo EL. Flutamide monotherapy as primary treatment in advanced prostatic carcinoma. Semin Oncol 1991; 18: 13-8.
52. Prout GR Jr, Keating MA, Griffin PP, Schiff SF. Long-term experience with flutamide in patients with prostatic carcinoma. Urology 1989; 34 (suppl): 37-45.
53. Sogani PC, Whitmore WF Jr. Experience with flutamide in previously untreated patients with prostatic cancer. J Urol 1979; 122: 640-3.
54. Boccon-Gibod L. Nonsteroidal antiandrogen monotherapy of metastatic cancer of the prostate. Eur Urol 1993; 24 (suppl 2): 77-80.
55. Chang A, Yeap B, Davis T, et al. Double-blind, randomized study of primary hormonal treatment of stage D2 prostate carcinoma: flutamide versus diethylstilbestrol. J Clin Oncol 1996; 14: 2250-7.
56. Wysowski DK, Freiman JP, Tourtelot JB, Horton ML 3d. Fatal and nonfatal hepatotoxicity associated with flutamide. Ann Intern Med 1993; 118: 860-4.
57. Mcload DG. Antiandrogenic Drug. Cancer 1993; 71 (3 suppl): 1046-9.
58. Decensi AU, Boccardo F, Guarneri D, et al. Monotherapy with nilutamide, a pure nonsteroidal antiandrogen, in untreated patients with metastatic carcinoma of the prostate. The Italian Prostatic Cancer Project. J Urol 1991; 146: 377-81.
59. Gomez JL, Dupont A, Cusan L, Tremblay M, Lafrie F. Simultaneous liver and lung toxicity related to the nonsteroidal antiandrogen nilutamide (Anandron): case report. Amer J Med 1992; 92: 563-6.
60. Kolvenbag GJ, Blackledge GR, Gotting-Smith K. Bicalutamide (Casodex) in the treatment of prostate cancer: history of clinical development. Prostate 1998; 34: 61-72.
61. Iversen P. Update of monotherapy trials with the new antiandrogen, casodex (ICI 176,334) Eur Urol 1994; 26 (suppl): 5-9.
62. Tyrrell CJ. Casodex: a pure non-steroidal antiandrogen used as monotherapy in advanced prostate cancer. Prostate 1992; 4 (suppl): 97-104.
63. Chodak G, Sharifi R, Kasimis B, Block NL, Macramalla E, Kennealey GT. Single-agent therapy with bicalutamide: a comparison with medical or surgical castration in the treatment of advanced prostate carcinoma. Urology 1995; 46: 849-55.
64. Bales GT, Chodak GW. A controlled trial of bicalutamide versus castration in patients with advanced prostate cancer. Urology 1996; 47(suppl

1A): 38-43.
65. Kaisary AV. Current clinical studies with a new nonsteroidal antiandrogen, Casodex. Prostate 1994; 5(suppl): 27-33.
66. Pont A, Williams PL, Azhar S, et al. Ketoconazole blocks testosterone synthesis. Arch Intern Med 1982; 142: 2137-40.
67. Young FM, Luderer WB, Rodgers RJ. The antioxidant beta-carotene prevents covalent crosslinking between cholesterol side-chain cleavage cytochrome P450 and its electron donor, adrenodoxin, in bovine luteal cells. Mol Cell Endocrinol 1995; 109: 113-8.
68. Crawford ED. Hormonal therapy of prostatic carcinoma: Defining the challenge. Cancer 1990; 66 (suppl): 1035-8.
69. Harper ME, Pike A, Peeling WB, Griffiths K. Steroidals of adrenal origin metabolized by human prostatic tissue both in vivo and in vitro. J Endocrinol 1974; 60: 117-25.
70. Geller J, Albert J, Loza D, Geller S, Stoeltzing W, de la Vega D. DHT concentrations in human prostate cancer tissue. J Clin Endocrinol Metab 1978; 46: 440-4.
71. Geller J, Albert JD, Nachtsheim DA, Loza D. Comparison of prostatic cancer tissue dihydrotestosterone levels at the time of relapse following orchiectomy or estrogen therapy. J Urol 1984; 132: 693-6.
72. Farnsworth WE, Brown JR. Androgen of the human prostate. Endocr Res Commun 1976; 3: 105-17.
73. Geller J, Albert J. Effects of castration compared with total androgen blockade on tissue dihydrotestosterone (DHT) concentration in benign prostatic hyperplasia (BPH). Urol Res 1987; 15: 151-3.
74. Labrie F. Intracrinology. Mol Cell Endocrinol 1991; 78: 113-8.
75. Huggins C, Scott WW. Bilateral adrenalectomy in prostatic cancer. Ann Surg 1945; 122: 1031-41.
76. Labrie F, Dupont A, Belanger A, et al. New approach in the treatment of prostate cancer: complete instead of partial ablation of androgens. Prostate 1983; 4: 579-94.
77. Crawford ED, Blumenstein BA. Proposed substages for metastatic prostate cancer. Urology 1997; 50: 1027.
78. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989; 321: 419-24.
79. Dijkman GA, Janknegt RA, De Reijke TM, Debruyne FM. Long-term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. International Anandron Study Group. J Urol 1997; 158: 160-3.
80. Eisenberger MA, Crawford ED, Wolf M, et al. Prognostic factors in stage D2 prostate cancer; important implications for future trials: results of a cooperative intergroup study (INT.0036). The National Cancer Institute Intergroup Study : 0036. Semin Oncol 1994; 21: 613-9.
81. Bertagna C, De Gery A, Hucher M, Francois JP, Zanirato J. Efficacy of the combination of nilutamide plus orchidectomy in patients with metastatic prostatic cancer. A meta-analysis of seven randomized double-blind trials (1056 patients). Br J Urol 1994; 73: 396-402.
82. Iversen P, Rasmussen F, Klarskov P, Christensen IJ. Long-term results of Danish Prostatic Cancer Group trial 86. Goserelin acetate plus flutamide versus orchiectomy in advanced prostate cancer. Cancer 1993; 72: 3851-4.
83. Tyrrell CJ, Altwein JE, Klippel F, et al. Multicenter randomized trial comparing Zoladex with Zoladex plus flutamide in the treatment of advanced prostate cancer. Survival update. Cancer 1993; 72: 3878-9.
84. Boccardo F, Pace M, Rubagotti A, et al. Goserelin acetate with or without flutamide in the treatment of patients with locally advanced or metastatic prostate cancer. The Italian Prostatic Cancer Project (PONCAP) Study Group. Eur J Cancer 1993; 29 A: 1088-93.
85. Ferrari P, Castagnetti G, Ferrari G, Pollastri CA, Tavoni F, Dotti A. Combination treatment in M1 prostate cancer. Cancer 1993; 72: 3880-5.
86. Klijn JG, de Voogt HJ, Studer UE, Schroder FH, Sylvester R, De Pauw M. Short-term versus long-term addition of cyproterone acetate to buserelin therapy in comparison with orchidectomy in the treatment of metastatic prostate cancer. European Organization for Research and Treatment of Cancer--Genitourinary Group. Cancer 1993; 72: 3858-62.
87. Robinson MR. A further analysis of European Organization for Research and Treatment of Cancer protocol 30805. Orchidectomy versus orchidectomy plus cyproterone acetate versus low-dose diethylstilbestrol. Cancer 1993; 72: 3855-7.
88. Denis L, Smith PH, De Moura JL, et al. Orchidectomy vs. Zoladex plus flutamide in patients with metastatic prostate cancer. The EORTC GU Group. Eur Urol 1990; 18 (suppl 3): 34-40.
89. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: An overwiev of 22 randomized trials with 3283 deaths in 5710 patients. Lancet 1995; 346: 265-9.
90. Waxman J, Pandha H, Crawford ED, Labrie F, Quartry P. Anti androgen in treatment of prostate

cancer: letter to editor. Lancet 1995; 346: 1030-1.
91. Byar DP. The Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate. Cancer 1973; 32: 1126-30.
92. Daneshgari F, Crawford ED. Endocrine therapy of advanced carcinoma of prostate. Cancer 1993; 71: 1089-97.
93. Denis L, Murphy GP. Overview of phase III trials on combined androgen treatment in patients with metastatic prostate cancer. Cancer 1993; 72: 3888-95.
94. Kramolowski EV. The value of testosterone deprivation in stage D1 carcinoma of the prostate. J Urol 1988; 139: 1242-4.
95. Zagars GK, Sands ME, Pollack A, von Eschenbach AC. Early androgen ablation for stage D1 (N1 to N3, M0) prostate cancer: prognostic variables and outcome. J Urol 1994; 151: 1330-3.
96. van den Ouden D, Tribukait B, Blom JH, et al. Deoxyribonucleic acid ploidy of core biopsies and metastatic lymph nodes of prostate cancer patients: impact on time to progression. The European Organization for Research and Treatment of Cancer Genitourinary Group. J Urol 1993; 150: 400-6.
97. The Medical Research Council Prostate Cancer Working Party Investigators Group: Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council trial. Br J Urol 1997; 79: 235-46.
98. Kelly WK, Scher HI. Prostate specific antigen decline after antiandrogen ablation: the flutamide ablation syndrome. J Urol 1993; 149: 607-9.
99. Dupont A, Gomez JL, Cusan L, Koutsilieris M, Labrie F. Response to flutamide ablation in advanced prostate cancer in progression under combination therapy. J Urol 1993; 150: 908-13.
100. Scher HI, Zhang ZF, Nanus D, Kelly WK. Hormone and antihormone ablation: implications for the management of androgen-independent prostate cancer. Urology 1996; 47(Suppl 1A): 61-9.
101. Small EJ, Carroll PR. Prostate-specific antigen decline after casodex ablation: evidence for an antiandrogen ablation syndrome Urology 1994; 43: 408-10.
102. Dawson NA, McLeod DG. Dramatic prostate specific antigen decrease in response to discontinuation of megestrol acetate in advanced prostate cancer: expansion of the antiandrogen ablation syndrome. J Urol 1995; 153: 1946-7.
103. Bissada NK, Kaczmarek AT. Complete remission of hormone refractory adenocarcinoma of the prostate in response to ablation of diethylstilbestrol. J Urol 1995; 153: 1944-5.
104. Veldscholte J, Berrevoets CA, Brinkmann AO, Grootegoed JA, Mulder E. Anti-androgens and the mutated androgen receptor of LNCaP cells: differential effects on binding affinity, heat-shock protein interaction, and transcription activation. Biochemistry 1992; 31: 2393-9.
105. Bruchovsky N, Rennie PS, Coldman AJ, Goldenberg SL, To M, Lawson D. Effects of androgen ablation on the stem cell composition of the Shionogi carcinoma. Cancer Research 1990; 50: 2275-82.
106. Klotz LH, Herr HW, Morse MJ, Whitmore WF Jr. Intermittent endocrine therapy for advanced prostate cancer. Cancer 1986; 58: 2546-50.
107. Akakura K, Bruchovsky N, Goldenberg SL, Rennie PS, Buckley AR, Sullivan LD. Effects of intermittent androgen suppression on androgen-dependent tumors: apoptosis and serum prostate-specific antigen. Cancer 1993; 71: 2782-90.
108. Goldenberg SL, Bruchovsky N, Gleave ME, Sullivan LD, Akakura K. Intermittent androgen suppression in the treatment of prostate cancer: a preliminary report. Urology 1995; 45: 839-45.
109. Isaacs JT, Kyprianou N. Development of androgen-independent tumor cells and their implication for the treatment of prostatic cancer. Urological Res 1987; 15: 133-8.
110. Rennie PS, Bruchovsky N, Coldman AJ. Loss of androgen dependence is associated with an increase in tumorigenic stem cells and resistance to cell-death genes. J Steroidal Biochem Mol Biol 1990; 37: 843-7.
111. Furuya Y, Sato N, Akakura K, et al. Paracrine growth stimulation of androgen-responsive Shionogi Carcinoma 115 by its autonomous subline (Chiba Subline 2). Cancer Res 1990; 50: 4979-83.
112. Colombel M, Olsson CA, Ng PY, Buttyan R. Hormone-regulated apoptosis results from reentry of differentiated prostate cells onto a defective cell cycle. Cancer Research 1992; 52: 4313-9.
113. Debbas M, White E. Wild-type p53 mediates apoptosis by E1A, which is inhibited by E1B. Genes Dev 1993; 7: 546-754.
114. McDonnell TJ, Troncoso P, Brisbay SM, et al. Expression of the protooncogene bcl-2 in the prostate and its association with emergence of androgen-independent prostate cancer. Cancer Res 1992; 52: 6940-4.
115. Trapman J, Brinkmann AO. The androgen receptor in prostate cancer. Pathol Res Pract 1996; 19: 752-60.
116. Koivisto P, Visakorpi T, Kallioniemi OP. Androgen receptor gene amplification: a novel molecular mechanism endocrine therapy resistance in human prostate cancer. Scand J Clin Lab Invest 1996; 226 (suppl): 57-63.

การรักษามะเร็งต่อมลูกหมากที่มีการกระจายโดยการกำจัดฮอร์โมน

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ในปัจจุบันมะเร็งต่อมลูกหมากเป็นมะเร็งที่พบมากที่สุดในผู้ชายในซีกโลกตะวันตก ในประเทศไทยพบว่ามะเร็งต่อมลูกหมากพบมากเป็นอันดับที่ 10 ในบรรดามะเร็งที่พบมากที่สุดในชายไทย อย่างไรก็ดีพบว่ามะเร็งต่อมลูกหมากในชายไทยดูเหมือนจะมีอุบัติการณ์สูงมากขึ้นตั้งแต่มีการตรวจระดับ พี เอส เอ ซึ่งเป็นเอนไซม์ที่ถูกสร้างขึ้นโดยเซลล์ต่อมลูกหมาก เพราะว่ามะเร็งต่อมลูกหมากระยะแรกๆ มักไม่มีอาการแสดงออก ดังนั้นชายไทยที่เป็นมะเร็งต่อมลูกหมากที่มาหาแพทย์มักเป็นระยะที่มีการกระจายแล้ว

จากการศึกษาของ Huggins และ Hodges ในปี ค.ศ. 1941 พบว่าการกำจัดฮอร์โมนเพศชายแอนโดรเจนเป็นการรักษามาตรฐานของมะเร็งต่อมลูกหมากที่มีการกระจายแล้ว แปดสิบเปอร์เซนต์ของผู้ป่วยจะตอบสนองต่อการกำจัดฮอร์โมนเพศชาย ดังนั้นการรักษามะเร็งต่อมลูกหมากในไทยนั้น การกำจัดฮอร์โมนเพศชายจึงมีความสำคัญมากในเวชปฏิบัติของแพทย์ทางเดินปัสสาวะ

ดังนั้น บทความวิจารณ์ต่อไปนี้จะได้สาธยายถึงผลของการกำจัดฮอร์โมนเพศชายอย่างเดียว และเหตุผลอันสมควร, ผลการรักษา ตลอดจนการรักษาที่ใช้วิธีการกำจัดฮอร์โมนเพศชายแบบผสมผสาน ในการรักษามะเร็งต่อมลูกหมากที่มีการกระจาย

คำสำคัญ : มะเร็งต่อมลูกหมากที่มีการกระจาย, การกำจัดฮอร์โมน, บทความปริทรรศน์

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