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Review

Major impact of hormonal therapy in localized prostate cancer—death can already be an exception

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Abstract

For about 50 years, androgen blockade in prostate cancer has been limited to monotherapy (surgical castration) or high doses of estrogens in patients with advanced disease and bone metastases. The discovery of medical castration with LHRH agonists has led to fundamental changes in the endocrine therapy of prostate cancer. In 1979, the first prostate cancer patient treated with an LHRH agonist received such treatment at the Laval University Medical Center. A long series of studies have clearly demonstrated that medical castration with an LHRH agonist has inhibitory effects on prostate cancer equivalent to those of surgical castration. The much higher acceptability of LHRH agonists has been essential to permit a series of studies in localized disease. Based upon the finding that the testicles and adrenals contribute approximately equal amounts of androgens in the human prostate, the combination of medical (LHRH agonist) or surgical castration associated with a pure antiandrogen (flutamide, nilutamide or bicalutamide) has led to the first demonstration of a prolongation of life in prostate cancer, namely a 10–20% decreased risk of death according to the various metaanalyses of all the studies performed in advanced disease. In analogy with the other types of advanced cancers, the success of combined androgen blockade in metastatic disease is limited by the development of resistance to treatment. To avoid the problem of resistance to treatment while taking advantage of the relative ease of diagnosis of prostate cancer at an "early" stage, the much higher acceptability of LHRH agonists has permitted a series of studies which have demonstrated a major reduction in deaths from prostate cancer ranging from 31% to 87% at 5 years of follow-up in patients with localized or locally advanced prostate cancer. Most importantly, recent data show that the addition of a pure antiandrogen to an LHRH agonist in order to block the androgens made locally in the prostate leads to a 90% long-term control or probable cure of prostate cancer.

Keywords: Combined androgen blockade; Monotherapy; LHRH agonists; Pure antiandrogens; Localized disease; Androgens; Prostate cancer; Early diagnosis; Intracrinology

Contents

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1. Introduction

Prostate cancer is the most frequently diagnosed cancer and the second cause of cancer death in men in North America [1]. In fact, one out of eight men will be diagnosed with prostate cancer during his lifetime. At such a rate, prostate cancer will kill more than 3,000,000 men among the male population presently living in the United States, while more than 200,000 men die annually worldwide from prostate cancer. The medical and social consequences of this disease are comparable to those of breast cancer in women. Prostate cancer is thus a major challenge in urgent need of significant improvement in diagnosis and treatment.

2. Prostate cancer deaths are decreasing

Death rates from prostate cancer have dropped by 17% in the United States between 1994 and 2003 (Fig. 1). This decrease in prostate cancer death coincides with the routine use of the prostate specific antigen (PSA) test. These numbers are those estimated or predicted by the American Cancer Society. This decrease in prostate cancer death is a major improvement since it corresponds to a decrease of 6002 deaths from prostate cancer in 2003 compared to 1994. This decrease in cancer deaths can only be due to improved diagnosis and better treatment. This certainly indicates that more cases of localized disease have been treated since we know that we cannot have such a positive impact on cancer deaths in advanced metastatic disease.

3. Two equally important sources of androgens in men

An important advance in our understanding of the biology and endocrinology of prostate cancer and its impact on cancer treatment is the observation that humans and some other primates are unique among animal species in having adrenals that secrete large amounts of the inactive precursor steroids dehydroepiandrosterone (DHEA), its sulfate DHEA-S, and some androstenedione (4-dione), which are converted into potent androgens in a large series of peripheral tissues, including the prostate (Fig. 2). In fact, the plasma concentration of DHEA-S secreted by the adrenals in adult men is 100–500 times higher than that of testosterone [2], the main secretory product of the testicles. Such high circulating levels of DHEA-S (and also DHEA) provide high amounts of the prehormones or precursors required for conversion into active androgens in the prostate as well as in other peripheral intracrine tissues.

The local synthesis of active steroids in peripheral target tissues has been called intracrinology [3–5]. The active androgens made locally in the prostate exert their action by interacting with the androgen receptor in the same cells where their synthesis takes place without being released in the extracellular environment or the general circulation. Contrary to the previous belief that the testes are responsible for 90–95% of total androgen production in men (as suggested by the decrease in serum testosterone after castration), it is now well demonstrated that the prostatic tissue efficiently transforms

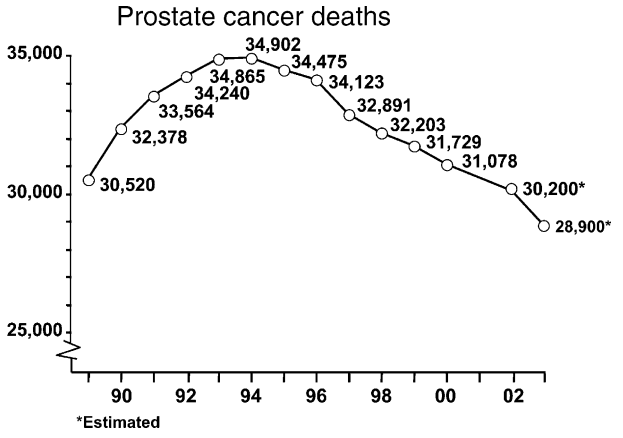

Fig. 1. Death rates from prostate cancer have dropped by 17% in the United States since 1994 [1].

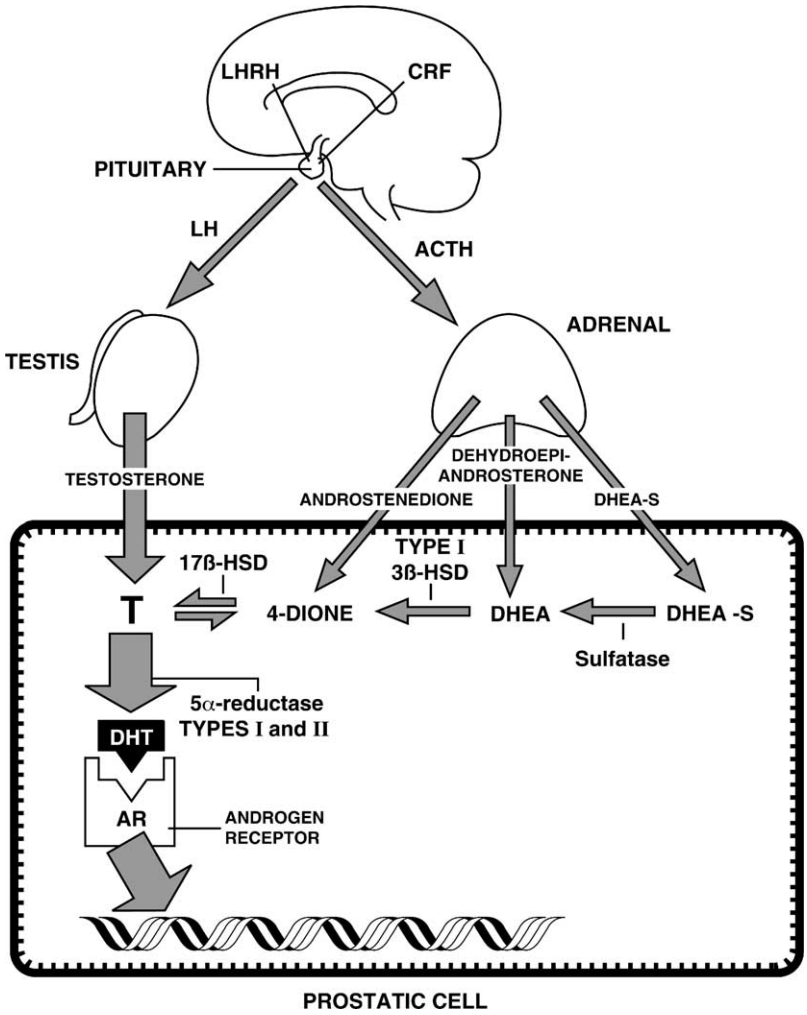

Fig. 2. Intracrine activity of the human prostate or biosynthetic steps involved in the formation of the active androgen dihydrostestosterone (DHT) from testicular testosterone as well as from the adrenal precursors dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), and androstenedione (Δ^4-dione) in human prostatic tissue. 17β-HSD = 17β-hydroxysteroid dehydrogenase; 3β-HSD = 3β-hydroxysteroid dehydrogenase/Δ^5–Δ^4-isomerase. The widths of the arrows indicate the relative importance of the sources of DHT in the human prostate: 60% originating from the testes and 40% from the adrenals in 65-year-old men. The testis secretes testosterone (T), which is transformed into the more potent androgen DHT by 5α-reductase in the prostate. Instead of secreting T or DHT directly, the adrenal secretes very large amounts of DHEA, DHEA-S, and Δ^4-dione, which are transported in the blood to the prostate and other peripheral tissues. These inactive precursors are then transformed locally into the active androgens T and DHT. The enzymatic complexes DHEA sulfatase, 3β-HSD, 17β-HSD, and 5α-reductase are all present in the prostatic cells, thus providing 40% of total DHT in this tissue [107].

the inactive steroid precursors DHEA-S, DHEA, and 4-dione into the active androgens testosterone and DHT locally in peripheral tissues without significant release of the active androgen in the circulation. In fact, the prostate makes its own androgens at a level comparable to the androgens of testicular origin.

The human steroidogenic pathway is composed of 15 main steps transforming cholesterol into the five classes of active hormonal steroids, namely androgens (testosterone and DHT), estrogens (estradiol and 5-androstenediol), progesterone, glucocorticoids (cortisol or corticosterone) and mineralocorticoids (aldosterone), as well as their inactive sulfated and glucurunosyltated derivatives (Fig. 3). So far, 30 human genes have been found to encode enzymes of the steroidogenic pathway. Such a large number of steroidogenic enzyme isoforms allows tissue-specific expression and thus local control of steroid formation according to local needs dictated by intracellular and extracellular signals. These control mechanisms permit local regulation of steroid action independently from the circulating levels of these steroids.

The formation and inactivation of androgens and estrogens is under fine control by a series of enzymes which reduce (activate) or oxidize (inactivate) the C17 position of C19 (androgens) or C18 (estrogens) steroids. At the present time, eleven human 17β-hydroxysteroid dehydrogenases (17β-HSDs) are known and can be divided into two functional groups. Those of the first group are represented by types 1, 3, 5 and 7 17β-HSDs which prefer NADPH as cofactor and catalyze the reduction of 17-ketosteroids (inactive form) into 17β-hydroxysteroids (active form) (see Fig. 3). On the other hand,

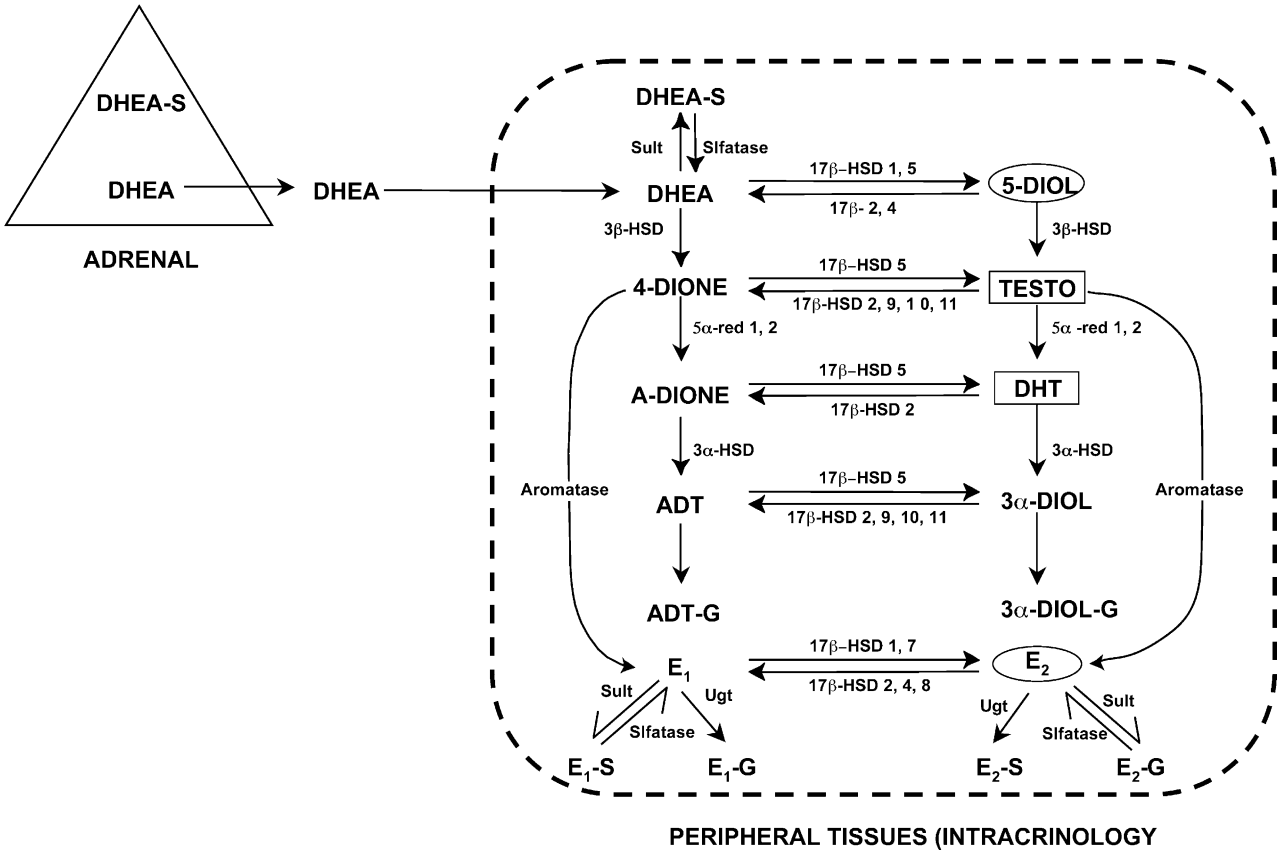

Fig. 3. Human steroidogenic and steroid-metabolizing enzymes in peripheral intracrine tissues.

the members of the second group represented by types 2, 4, 6, 8, 9, 10 and 11 17β-HSDs, function as dehydrogenases or inactivating enzymes. These enzymes prefer NAD+ as cofactor and catalyze the oxidation of 17β-hydroxysteroids.

3.1. Steroidogenic enzymes

Type 5 17β-HSD: In analogy with type 3 17β-HSD, this enzyme catalyzes the transformation of 4-dione into testo, although its tissue distribution is very different [6]. It is believed that this enzyme plays a crucial role in the formation of testo in all tissues in women and in peripheral tissues in men [7,8]. This enzyme is most likely responsible for the virilization of young adult males deficient in type 3 17β-HSD [9] at the time of puberty when the secretion of DHEA by the adrenals increases.

Type 7 17β-HSD: It is of interest that type 7 17β-HSD [10], the other enzyme that catalyzes the transformation of E1 into E2, is expressed in all tissues at a somewhat higher level than type 1 17β-HSD, including the ovary.

Types 9, 10 and 11 17β-HSDs [11–13]: Types 9, 10 and 11 17β-HSDs [11–13] are enzymes which catalyze the oxidation of the 17β-hydroxy 5α-reduced steroids, and can also transform 5α-androstane-3α,17β-diol into 5α-androstane-3α-ol-17-one (androsterone). These enzymes could play an important role in the inactivation of DHT.

The best known action of *5α-reductase* (*5α-red*) is the transformation of the weak androgen testo into the most potent natural androgen, namely DHT. On the other hand, the best known activity of *3α-HSDs* [14,15] is the inactivation of the potent androgen DHT into 3α-DIOL. It is generally thought that these enzymes are highly expressed in androgen-sensitive tissues, the prostate being the best known example [16].

3.2. Steroid-inactivating enzymes

There is also good evidence that the DHT formed in peripheral tissues is essentially metabolized locally before its appearance in the circulation [17,18]. Phase I DHT catabolites include androstanedione, androsterone (ADT), epiandrosterone, androstane-3α,17β-diol (3α-DIOL) and androstane-3β,17β-diol, which are formed by the action of a series of 3α/β-HSDs and 17β-HSD isoforms (Fig. 3) [19–22]. However, most if not all of the androgen-target tissues express HSD isoforms that are capable of back converting the Phase I metabolites into DHT, thus suggesting that a fine regulation of these enzymes is extremely important for controlling the concentration of DHT in androgen-target tissues [22].

The serum levels of the conjugates are increased after oral or topical administration of DHEA or 4-dione in the pres-

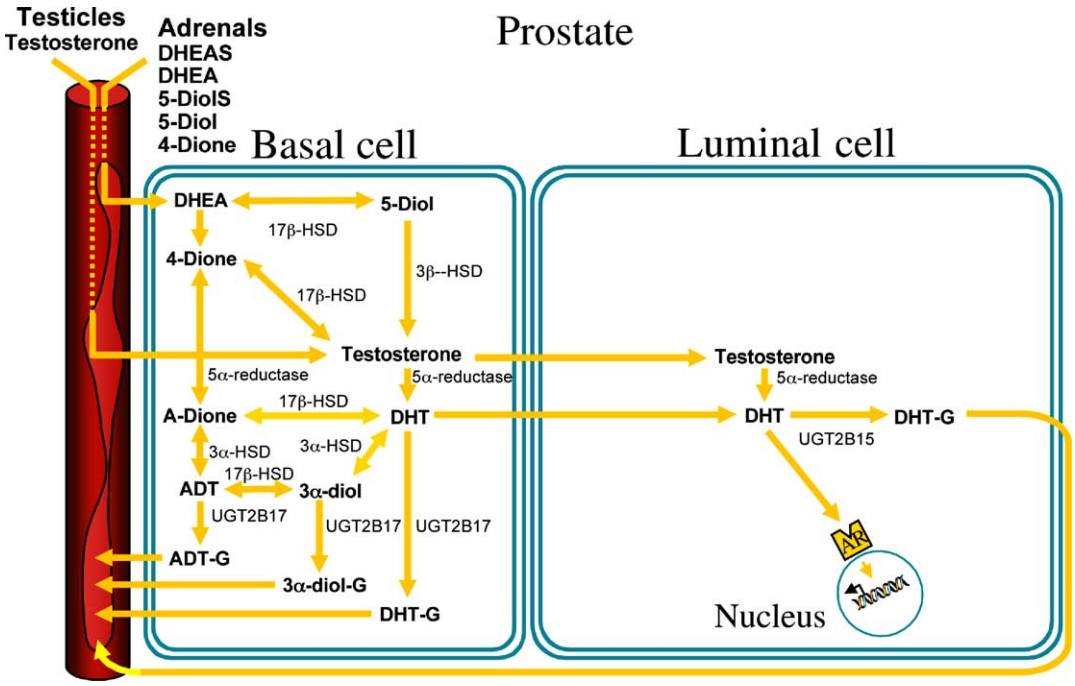

Fig. 4. Distribution of the steroidogenic and steroid-metabolizing enzymes in the human prostate.

ence of no change or minimal change in the blood levels of nonconjugated androgen metabolites [23]. These observations further support the concept that 5α-reduced androgen glucuronides found in the circulation are produced in situ in peripheral tissues after conversion of the adrenal and/or gonadal steroid precursors into DHT first and, subsequently, into Phase I DHT metabolites without release of these intermediate steroid precursors and metabolites into the circulation [4,5,17,18]. Consequently, the glucuronidation of Phase I metabolites by UDP-glucuronosyltransferase (UGT) enzymes in androgen-sensitive tissues should be considered as the end of the androgenic signal. In the circulation, two major Phase II DHT metabolites, namely 3α-DIOLG and ADTG, have been identified, but low amounts of DHTG and 3β-DIOLG were also detected [3–5].

3.3. UGT enzymes

Conjugation of compounds, including steroids, by glucuronidation is a pathway that has been found in all vertebrates studied to date. More than 45 different UGT cDNA clones have been isolated from seven mammalian species, including 18 human UGT clones [24,25].

3.4. UGT2B enzymes in the human prostate

In the human prostate, the alveoli are composed of two cell types. The basal cells are small cells lining the periphery of the alveoli, whereas the luminal cells are large columnar cells in contact with the alveolar lumen. The two cell types play distinct roles in androgen formation and action (Fig. 4). The expression of type 1 3β-HSD, type 5 17β-HSD and types 1 and 2 5α-reductase is detected in the basal cells, whereas in the luminal cells, where the androgen receptor is exclusively observed, mostly 5α-reductase activity is found [7,26]. After castration, DHT concentrations in the prostate are reduced by about 60%, thus indicating that testosterone precursors, such as DHEA, are responsible for an important proportion of DHT in the prostate [6]. It is reasonable to suggest that DHT is formed locally in luminal cells from testosterone, which is provided by the circulation and/or metabolism of circulating adrenal steroid precursors (DHEA and 4-dione) in basal cells. Enzymes of the phase I DHT catabolism are also present in basal cells, but they are not detected in luminal cells, which occupy the largest proportion of the human prostate [19,27,28]. This absence of phase I catabolic enzymes in luminal cells favors large concentrations of DHT. Indeed, DHT concentrations in the prostate exceed by almost 10-fold those of testosterone and phase I DHT metabolites [29,30]. The two-cell mechanism provides the basis for the specific control of testosterone and DHT levels in the prostatic tissue.

To support the presence of conjugating activity in this tissue, large concentrations of 3α-DIOLG and ADTG were also reported [7]. Finally, the expression of UGT2B15 and B17 was subsequently established in the prostate [31]. The UGT2B17 protein is detected in basal cells, whereas UGT2B15 is only observed in luminal cells [32]. It is probable that 3α-DIOL and ADT formed in basal cells are easily converted to glucuronides by UGT2B17, whereas the action of UGT2B15 would be limited to DHT in the luminal cells. Taking into account the low levels of UGT2B15 protein found in the prostate, this situation favors high concentrations of DHT in this tissue, in agreement with previous biochemical

observations on the intraprostatic levels of DHT. In addition, because the affinity of DHT for the androgen receptor is approximately 1000-fold higher than that for UGT2B15, it is believed that UGT2B15 might conjugate only a fraction of the accumulated DHT formed in the luminal cells.

3.5. UGT2B15 and prostate cancer

The co-localization of the 5α-reductase enzyme, the androgen receptor and UGT2B15 enables the fine-tuning of the intracellular DHT concentration and action. Because two polymorphic forms of UGT2B15 exist with different efficacy on DHT conjugation, it was reasonable to postulate that the presence of the low-conjugating allele UGT2B15(D^{85}) has an effect on DHT concentrations [8]. Two groups have recently conducted epidemiological studies to determine the potential role of the *UGT2B15* gene in prostate cancer risk. The first study was performed with 64 pathologically confirmed prostate cancers and 64 controls recruited in the Arkansas area [33]. Distribution of the UGT2B15 (D^{85}) allele in prostate cancer was significantly higher (40.6%) compared with control (18.8%) and the risk of developing cancer in homozygous patients with the D^{85} allele was three-fold higher. However, in the second study conducted with 380 Caucasians from Austria, including 190 cases with prostate cancer and 190 patients suffering from benign prostate hyperplasia, no association could be demonstrated between the two alleles and prostate cancer [34]. It is clear that further studies are required for a better understanding of the role of UGT2B15 and other polymorphisms in prostate cancer development.

In our genomic program, we are measuring the levels of mRNAs encoding all these enzymes which amount to 45 steroidogenic and steroid metabolizing enzymes. It is of interest to mention that all the enzymes expressed in the human are also found in the same peripheral tissues in the mouse. Thus, while the mouse separated from man 75 million years ago, it is remarkable that all the enzymes responsible for the formation and inactivation of androgens in peripheral tissues are also expressed in the mouse, thus strongly supporting the important role of these enzymes, not only in the human and the other primates, but also in lower animal species.

An important point to make is that testosterone and DHT are made locally and the amount of testosterone and DHT which are found in the circulation is not a reliable parameter of the true exposure to androgens in target tissues. In fact, DHT, as well as testosterone, are inactivated locally in the prostate tissue to glucuronyl derivatives of testosterone, DHT, androstanediol and androsterone, these compounds are more water-soluble and are thus easily released into the circulation from which they are then eliminated, mostly by the bile, and then through the intestine. Accordingly, plasma sex steroid concentrations have very limited value for estimating what is going on in the peripheral tissues. The testis makes testosterone which can be directly measured in the circulation and it reaches the peripheral tissues through this vehicle. The adrenals, on the other hand, secrete a large amount of DHEA which is also released into the circulation through which it reaches the peripheral target intracrine tissues where it is transformed into testosterone and DHT. However, very little testosterone or DHT made from DHEA comes back into the circulation. In fact, these two steroids act locally and are inactivated locally mainly by glucuronosyl transferases. These glucuronyl derivatives are the steroids which can be easily measured in the blood, thus providing a proper estimate of the androgen milieu.

These explanations about the physiology of androgens in man are extremely important in order to choose the appropriate androgen blockade for the most efficient treatment of prostate cancer. In fact, the understanding of the two sources of androgens in men and their relative importance is crucial for the best choice of androgen blockade for the prostate cancer patients. We know that prostate cancer is highly androgen-sensitive. Accordingly, we should choose the best way to take advantage of this very important characteristic of prostate cancer. In fact, prostate cancer is the most sensitive of all cancers to hormonal therapy, even more than breast cancer which is already highly sensitive to hormonal therapy. The most scientifically based approach is to use an LHRH agonist, in order to block androgen secretion from the testicles or remove the testicles surgically. At the same time, however, the action of the androgens made locally in the prostate must be blocked with a pure antiandrogen.

The decision between medical and surgical castration is a matter of choice by the patient. In both cases, however, we are then left with the androgens of adrenal origin, namely DHEA which is converted to DHT in the prostate. In order to block the DHT made locally in the prostate, we can use the pure antiandrogens flutamide or nilutamide. Bicalutamide is also another pure antiandrogen which, in my opinion, has the same efficacy as flutamide or nilutamide, when used at the appropriate dose (150 mg or more daily).

Contrary to the previous erroneous belief that the testes are responsible for 95% of total androgen production in men, as suggested by simple measurement of circulating serum testosterone, it is now well demonstrated that the prostatic tissue efficiently transforms the inactive steroid precursors DHEA-S, DHEA, and 4-dione into the active androgen DHT (Fig. 2). In fact, the prostate synthesizes its own androgens (Fig. 3).

4. Medical castration with LHRH agonists

While the experiments performed in the rat were simply suggestive of an inhibitory effect of LHRH agonists on testicular functions, we discovered in 1979 that men are exquisitely sensitive to the inhibitory action of an LHRH agonist. We then studied the effect of administering the LHRH agonist buserelin to a patient suffering from stage B prostate cancer. Thus, in the first prostate cancer patient treated with an LHRH agonist, the 500-μg dose of the LHRH agonist administered intranasally twice daily caused 70% and 85% inhibitions of the

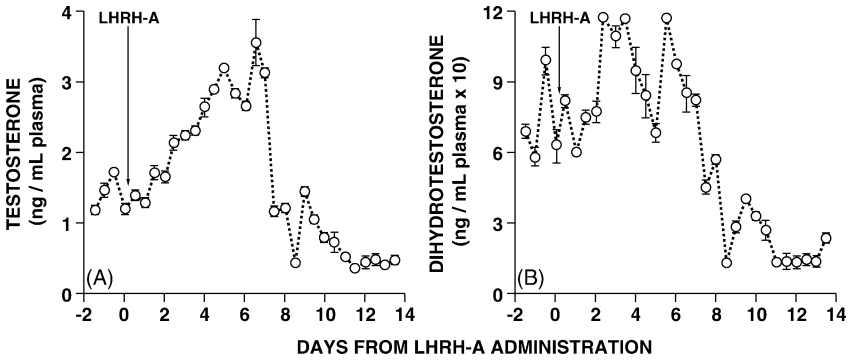

Fig. 5. Effect of twice daily intranasal administration of the LHRH agonist Buserelin on the serum levels of (A) testosterone and (B) DHT in a patient suffering from stage B prostate cancer [35].

serum levels of testosterone and dihydrotestosterone (DHT), respectively, as early as 2 weeks after the start of therapy [35] (Fig. 5). This marked inhibition of the serum concentration of both testosterone and DHT followed an initial period of stimulation that lasted approximately 1 week.

The availability of a safe and highly efficient method of medical castration with LHRH agonists free of the side effects of estrogens and surgical castration has generated renewed interest in the treatment of prostate cancer and has stimulated an unprecedented number of clinical studies which rapidly led to the world-wide commercialization of a series of LHRH agonists having equivalent characteristics, mechanisms of action, and efficacy.

5. Combined androgen blockade in advanced disease

The first treatment shown to prolong life in prostate cancer is the combination of an LHRH agonist (blocker of androgen secretion by the testes) with a pure antiandrogen such as flutamide, nilutamide or bicalutamide (at the proper dose, namely at least 150 mg daily). When associated with castration which eliminates the androgens of testicular origin, these compounds sometimes called nonsteroidal antiandrogens block the action of the androgens produced locally in the prostate [2,36–43].

An interesting observation is that the first demonstration of the benefits of combined androgen blockade (CAB) on survival has been achieved in the most difficult group of patients to treat, namely those suffering from metastatic or advanced disease. Although the clinical data should be similar for bicalutamide, the two antiandrogens flutamide and nilutamide are the compounds shown in prospective and randomized studies, to prolong life, to increase the number of complete and partial responses, to delay progression, and to provide better pain control (thus improving quality of life) in metastatic prostate cancer when added to surgical or medical castration compared with castration alone [37–49]. In the first large scale randomized study, patients who were treated with flutamide and the LHRH agonist Lupron lived, on average, 7.3

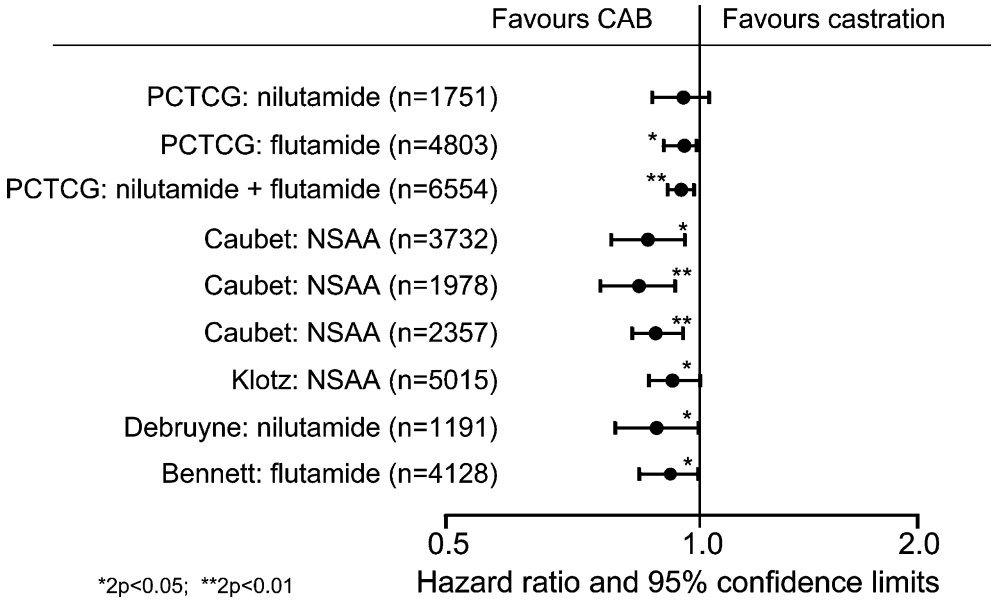

Fig. 6. Summary of metaanalyses comparing combined androgen blockade (combination of medical or surgical castration) vs. medical or surgical castration associated with a pure antiandrogen or non steroidal antiandrogen (NSAA), namely Flutamide or Nilutamide. Adapted from Klotz et al. (2001).

months longer than those who received Lupron plus placebo [37].

Analysis of all the studies performed with flutamide and nilutamide associated with medical or surgical castration compared with castration plus placebo shows that overall survival is increased by an average of 3–6 months [37–40,44–48] (Fig. 6). Since about 50% of patients in that age group die from causes other than prostate cancer, this 3–6 month difference in overall survival translates into an average of 6–12 months of life gained when cancer-specific survival is analyzed. These additional months, or sometimes, years of life can be obtained by simply adding a pure antiandrogen (flutamide, nilutamide or bicalutamide at a proper dose) to castration. These data demonstrate the particularly high level of sensitivity of prostate cancer to androgen deprivation, considering that such statistically significant benefits on survival have been obtained, even at the very advanced stage of metastatic disease.

Bennett at al. (1999) have performed a meta-analysis of all peer-reviewed published randomized controlled trials comparing treatment with flutamide in association with medical (LHRH agonist) or surgical castration versus castration alone in advanced prostate cancer. Nine studies with 4128 patients were included in the analysis which demonstrated a statistically significant 10% improvement in overall survival with the combination therapy using flutamide compared with castration alone. Similar benefits have been obtained in favor of flutamide plus castration versus castration alone in the Prostate Cancer Trialist's Collaborative Group (PTCTG), 2000.

In fact, as illustrated in Fig. 6, all the metanalyses of all the data have shown significant ($2p < 0.05$) or highly significant ($2p < 0.01$) advantages of combined androgen blockade versus castration alone in advanced prostate cancer [39–41,45,48,49]. However, when the studies providing the most rigorous data are analyzed [45], a 20% advantage in overall survival is observed.

The only negative effect observed following the addition of an antiandrogen to castration has been found with cyproterone acetate (CPA) [48] The explanation is that CPA does not meet the criteria needed to be considered part of combined androgen blockade since this compound is not a pure antiandrogen and was therefore excluded at the beginning from the definition of combined androgen blockade [2,36]. In fact, preclinical studies [50,51] have clearly shown that CPA has mixed antiandrogenic-androgenic activities. For example, Plante et al. [51] found that steroidal compounds (i.e. chlormadinone acetate, megestrol acetate, cyproterone acetate and medroxyprogesterone acetate) stimulate androgen-sensitive tumour growth in Shionogi mammary carcinoma, while flutamide, a pure antiandrogen, has no such stimulatory effect. It is thus not surprising to find in the clinical studies summarized in the PCTCG meta-analysis [48], that the addition of CPA to castration, not only had no benefit but, on the contrary, caused a significant increase in the death rate (relative risk = 1.13 (S.D. 0.06), $2p = 0.04$) [48,52].

It is of interest to recall, as recently published by Aprikian et al. [42] that the cost per month of prolonged survival in prostate cancer achievable with the simple addition of a non-steroidal antiandrogen to castration (LHRH agonist or orchiectomy) is 50% that of vinorelbine for lung cancer, 10% of the cost of renotecan for colon cancer and 10% of the cost of trastuzumab for breast cancer. Moreover, the nonsteroidal antiandrogens have minimal toxicity when added to castration while vinorelbine and irinotecan are associated with severe grade 3 and 4 clinical toxicities and trastuzumab has cardiac side effects when associated with anthracyclines.

In a recent editorial Klotz [43] asked how the 10% reduction in the risk of overall death at 5 years well illustrated in the metaanalyses of 27 prospective and randomized studies [39,48] has been discounted? Could this be related to highly questionable "opinions" suggesting that the benefits of combined androgen blockade are "of negligible clinical significance" [53]. As mentioned by Klotz, such "an opinion cannot be excused by the acknowledgement that this is an opinion". It is very difficult or impossible to agree with some defenders of the status quo who say that a 3–6-month increase in overall survival in patients with metastatic prostate cancer is "of questionable clinical significance" (Report of the Blue Cross-Blue Shield Association Technology Evaluation Center). Very few patients would agree with such a statement. It is somewhat incredible to read that the 7.3 months of life added by flutamide in the National Cancer Institute (NCI) study "is not viewed as clinically of great importance" [54]. I do not believe that many patients would agree with this surprising judgment of Dr. Raghavan [54]. A persistent problem in the field of prostate cancer is the lack of understanding of the difficulty in achieving a major difference in survival (as with any type of cancer) when the treatment is started at the advanced metastatic stage. In fact, these opinions are simply wrong and do not take into account the fact that the months of life saved by the simple addition of a well tolerated antiandrogen to castration permits a statistically significant or highly significant prolongation of life according to all the metaanalyses performed [39–43,45,48,49,55]. Moreover, this negative opinion does not take into account the fact that the benefits observed are in patients with advanced disease where the benefits should be compared with other types of cancer and most importantly, it does not take into account the role of the patient who should be the one who decides if he wants added months of good quality of life with combined androgen blockade. As Klotz said: "We should embrace the modest survival benefit of combined androgen blockade in advanced prostate cancer and offer it to the appropriate patients."

In addition, as mentioned earlier, all the studies have shown that the decrease in bone pain is more rapid and complete and that progression of the cancer occurs later, thus improving quality of life, when combined androgen blockade is used compared to monotherapy. Moreover, this is the only treatment shown to prolong life in advanced disease. There is no other choice. In addition, there are no treatments

of similarly advanced cancers that provide 3–6 months of prolongation of life with such a good quality of life.

To the living population of males in the United States, where 3 million are expected to die from prostate cancer, 6 additional months of life correspond to the addition of 1.5 million years of life, while 12 additional months correspond to 3.0 million years of life.

6. Today, prostate cancer can be diagnosed at the clinically localized stage in more than 95% of cases

Despite the progress achieved in the treatment of advanced or metastatic prostate cancer using LHRH agonists [35,56] and especially with combined androgen blockade [36,37,39,40,45–48], it is well recognized that the only possibility of a significant reduction in prostate cancer mortality is the treatment of localized disease [57]. It is reasonable to suggest that the observed decrease in deaths from prostate cancer is due to earlier diagnosis with serum PSA [58,59] and transrectal ultrasound of the prostate [60] coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy, and endocrine therapy [57,61–64].

Since prostate cancer almost invariably develops insidiously without signs or symptoms until the non curable stage of bone metastases is reached, early treatment cannot be achieved without efficient screening in asymptomatic men. In the first prospective and randomized study of screening for prostate cancer, namely the Laval University Prostate Cancer Screening Program started in 1988 in Quebec City among 46,486 men aged 45–80 years, it has been found that screening permits to diagnose 99% of prostate cancers at a clinically localized or potentially curable stage. Screening practically eliminates the diagnosis of metastatic and non curable disease [59,65].

As clearly indicated in our previous reports [59,65], the most cost-effective strategy for early diagnosis of prostate cancer is measurement of serum PSA as first line or as a prescreening test in order to identify the men who are at a higher risk of prostate cancer. The same conclusion of the high efficacy of PSA has been reached in two other large scale screening studies [66–68]. A similar conclusion has been reached by Hugosson et al. [69] who wrote: “PSA seems to be excellent as a prescreening test to identify the population at risk and which needs further evaluation [70,71]”. Screening provides a lead time of at least 6 years and thus permits “Early Treatment”. In our screening study, digital rectal examination was routinely done at first visit but not at follow-up visits where the PSA test was used alone. Transrectal ultrasound was performed if PSA and/or digital rectal examination was abnormal. With this screening approach used at more than 60,000 follow-up visits, 99% of cancers were diagnosed at a localized and therefore potentially curable stage, thus clearly demonstrating an efficacy which appears difficult to improve.

In the Quebec Screening study, only 1 out of 159 cancers (0.6%) diagnosed at follow-up visits was metastatic, thus permitting 99.4% of patients to be diagnosed at a localized stage [65]. Similarly, in the screening program of the American Cancer Society National Prostate Cancer Detection Program (ACS-NPCDP), only one of a total of 51 cancers diagnosed at follow-up visits was at a clinically advanced (C2) stage [72]. Hugosson et al. [69] have found that 97% of the cancers detected by screening were clinically localized. It is thus reasonable to suggest that if one follows the recommendations of the American Cancer Society [73] and of the American Urological Association [74], namely annual screening starting at the age of 50 years for the general population at no special risk, all subsequent visits should be equivalent to the follow-up visits of the present study, thus practically eliminating the diagnosis of metastatic prostate cancer [59].

Two other randomized screening trials for prostate cancer are ongoing, namely the Prostate, Lung, Colon, and Ovarian trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC). Results from those trials are not expected before year 2005. Moreover, their relatively late start carries the high risk of a significant contamination of the control group by screening.

7. Death from prostate cancer is reduced by two-thirds by screening and early treatment

In analogy with other cancer types, it is believed that our efforts should be concentrated on the diagnosis of prostate cancer at an early stage in order to be able to use curative therapies. Definitive proof of the benefits of screening for prostate cancer can only be obtained from prospective and randomized studies comparing the incidence of death from prostate cancer in a group of men screened and treated early versus a group of men receiving standard medical care. Accordingly, the Laval University Prostate Cancer Screening Program (LUPCSP) was started in November 1988 and its first analysis was published in 1999 [75]. The present results are those obtained after three additional years or after a total of 11 years of follow-up [76].

Of the 46,486 eligible men aged between 45 and 80 years included in the study started in November 1988, 31,133 men were invited by letter to be screened for prostate cancer while 15,353 were allocated to the control group of men not invited for screening. Ten (10) out of the 7348 screened men of the invited group died from prostate cancer, while 74 of the 14,231 men not invited for screening died from the disease. The exposures in the invited screened and the control unscreened groups are 50,433 and 141,535 man-years, respectively. Thus, over the 11-year period, the annual cause-specific death rate incidences are 19.8 and 52.3 per 100,000 man-years in the invited screened and the control unscreened groups, respectively (two sided p-value < 0.002, Fisher’s exact test). The prostate cancer death rate incidence is thus 62% lower in the group of men screened for prostate cancer compared with the men of the control group who followed standard medical practice (Fig. 7).

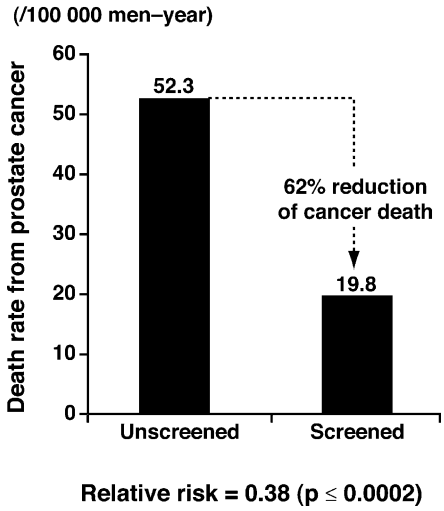

Fig. 7. Comparison of the incidence of death from prostate cancer in the men screened compared to the men unscreened for prostate cancer during the first 11 years of the study [76].

As strong support for the crucial role of early diagnosis and treatment, this first prospective and randomized prostate cancer screening study shows that early diagnosis combined with treatment of localized disease decreased death from prostate cancer by 62%. The present data are also in agreement with the 42% decrease observed in 1998 in the prostate cancer death rate in the Tyrol area where PSA screening was made available since 1993 compared to the rest of Austria where PSA screening was not offered [77]. Since about two-thirds of men were screened in Tyrol during that period, the 42% decreased death rate observed is similar to the 62% value measured in our study among the men who were all screened (Fig. 7) [76].

Clearly, the rational use of the presently available diagnostic and therapeutic approaches could decrease prostate cancer death by at least 50% [59,78]. As an example, between 1991 and 1999, the death rate from prostate cancer had decreased by 38% in the whole population of Québec City and its metropolitan area [79] while the death rate has decreased by 62% in the group of men who have been screened.

8. Monotherapy with an LHRH agonist decreases cancer deaths by at least one third in localized or locally advanced disease

Despite the recent advance in the treatment of metastatic prostate cancer using LHRH agonists [35,56] or surgical castration in association with a pure antiandrogen [36–49], it is well recognized that the only means of achieving an important reduction in prostate cancer mortality is treatment of localized disease [57]. In fact, it is reasonable to suggest that the recently observed decline in prostate cancer mortality is due to earlier diagnosis with serum PSA and transrectal ultrasound [60], coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy and endocrine therapy [57,61,62].

As indicated above, our research group at the Laval University Medical Research Center in Quebec City has discovered that medical castration can be easily and very efficiently achieved in men using the well tolerated luteinizing hormone-releasing hormone (LHRH) agonists [35,36,80,81]. Medical castration with an LHRH agonist is equivalent to orchiectomy for prostate cancer therapy [48]. In fact, in 11 trials where an LHRH agonist was used and in 17 trials where orchiectomy was used, no difference was seen on the response or survival rate [48]. Although equally efficient, orchiectomy is very difficult to accept in the absence of symptoms and signs of cancer. This novel approach has eliminated the previous limitations associated with blockade of testicular androgens by orchiectomy or high doses of estrogens [82]. These limitations are the psychological problems associated with surgical castration and the serious and even life-threatening side effects of high doses of estrogens on the cardiovascular system [83–85]. In fact, the availability of the well tolerated medical castration achieved with LHRH agonists [35] has opened the way to a much more acceptable treatment of prostate cancer, especially for localized disease where well tolerated therapies are particularly important for long term administration. In fact, only LHRH agonists could permit studies in localized disease.

The major source of controversy concerning early diagnosis and treatment of prostate cancer has been that, until recently, no prospective and randomized trial had shown statistically significant benefits on survival of treatment of localized prostate cancer [86,87]. Such an absence of studies has been erroneously interpreted as being equivalent to the presence of negative data while, in fact, negative data have never been obtained concerning the effect of androgen blockade in localized prostate cancer. In the absence of data, there are no effects. This has been the problem with the treatment of localized prostate cancer until 1997.

Most importantly, six prospective randomized trials have recently demonstrated an important prolongation of life achieved in localized prostate cancer patients treated with androgen blockade (Table 1). When considering deaths from prostate cancer at 5 years of follow-up, decreases ranging

Table 1
Effect of androgen blockade on prostate cancer death

Study	Benefits
EORTC [88]	77% decrease in cancer-specific death ($p = 0.01$)
RTOG [89]	37% decrease for Gleason score 8–10 ($p = 0.03$)
Quebec Screening Trial [78]	64% decrease in cancer-specific death ($p = 0.0002$)
Messing et al. [92]	81% decrease ($p = 0.001$)
Granfors et al. [91]	39% decrease in cancer-specific death ($p = 0.06$)
Hanks et al. [90]	59% decrease for Gleason score 8–10 ($p = 0.007$)

from 37 to 81% were observed in the various studies. In the European Organization of Research and Treatment of Cancer (EORTC) trial performed in stage T3 patients, overall survival at 5 years was increased from 62% in the group of patients who received radiation therapy alone to 79% (45% difference) in the group of patients who received androgen blockade using an LHRH agonist for 3 years and an antiandrogen for 1 month in association with radiotherapy [88]. Death from prostate cancer at 5 years was thus decreased by 77% by androgen blockade (Table 1). On the other hand, a 37% improvement in cancer-specific survival at 5 years had been found in RTOG trial 08531 in the subgroup of high Gleason score patients who received androgen blockade (LHRH agonist) indefinitely or until progression in association with radiotherapy versus radiotharepy alone [89]. In another study, a 54% decrease in cancer-specific death had been found in patients with an 8–10 Gleason score who had androgen blockade [90], while [91] have found a 39% decrease in cancer-specific death when castration was added to radiotherapy versus radiotherapy alone.

The results of another recent study are particularly interesting. In that study, of 98 men who had stage T2 prostate cancer at diagnosis but who were found to have pelvic lymph node metastases at radical prostatectomy, 47 had immediate hormonal therapy while 51 were followed until progression [92]. After a median follow-up of 7.1 years, 16 have died from prostate cancer in the deferred treatment group compared with only three in the immediate androgen blockade group for a 81% decrease in deaths from prostate cancer ($p = 0.001$), for men who had immediate hormonal therapy. The 62% decrease in the incidence of death from prostate cancer observed during the first 11 years of our randomized and prospective study on prostate cancer screening (Fig. 5) can only be due to the treatments used. In a study performed in 151 patients with T1b–T3 prostate cancer who received an LHRH agonist, the overall survival rates at 5 years were not different from that of the normal Japanese population, thus leading Akaza et al. [93] to suggest the usefulness of primary hormonal therapy for the control of localized and locally advanced prostate cancer.

It is not surprising that hormone therapy alone is more and more recognized as highly efficient in localized or locally advanced prostate cancer [94]. In fact, prostate cancer growing in the prostate or in the tissue surrounding the prostate is very different from cancer growing in the bones. Localized disease is much easier to treat by androgen blockade because it does not contain androgen-insensitive clones. Moreover, androgen insensitivity does not (or very rarely) develop in localized prostate cancer while the patients are receiving androgen blockade, contrary to the situation in metastatic disease where resistance to treatment almost always develops.

It is clear that the lifesaving benefits of androgen blockade in prostate cancer have been largely underestimated. In fact, the results obtained are quite remarkable and are similar or even better than the benefits observed for Tamoxifen in breast cancer. In agreement with the above-summarized data, a new analysis of existing clinical trial data attributes part of the improving outlook to early detection and prompt surgery, but mostly credits follow-up hormone therapy. “Hormonal treatment as a whole works ridiculously well” [95], reported by Arnst [96].

“Prostate cancer is usually treated with surgery or radiation, but a few cancer cells may remain and cause an often-fatal recurrence. Since the mid-1980s, oncologists have increasingly followed up with either surgical removal of the testes, or with newer anti-hormone drugs. Peto said that 74% of men who received hormone therapy were still alive 10 years later, compared with 62% of those who did not” [96]. Thus, in a metaanalysis of several studies (5000 men), hormonal treatment given immediately versus waiting until disease progressed, it was found that the risk of dying from prostate cancer within 10 years dropped by one-third [95]. It should be mentioned that the one third decrease in the risk of dying from prostate cancer is not the comparison between androgen blockade and placebo but between early versus late androgen blockade, thus suggesting that androgen blockade reduced the risk of dying from prostate cancer by more than one third. These results led R. Peto to the following conclusion: “Hormone treatment as a whole works much better than previously thought.”

9. The high probability of a cure of localized prostate cancer by combined androgen blockade

Despite the important advance observed with monotherapy (LHRH agonists) in localized prostate cancer, namely a one third to two-thirds reduction in deaths from prostate cancer, can we achieve better results? Based upon the observation that 50% of androgens are left in the prostate after castration alone, it is reasonable to suggest that better results can be achieved with the combination of an LHRH agonist and a pure antiandrogen.

With long-term treatment of localized prostate cancer with combined androgen blockade, the evidence obtained even indicates that long term control or cure of the disease can be obtained in the majority of patients [64]. In fact, while almost all studies performed so far in localized prostate cancer have used monotherapy (medical or surgical castration) [88–92], there are good reasons to believe that even better results can be obtained with combined androgen blockade [2,39,45,48,97,98]. The direct effect of combined androgen blockade on the volume of prostate cancer localized in the prostate is well illustrated in Fig. 8 which illustrates the results of two detailed anatomopathological studies performed in patients who had radical prostatectomies after 3 and 6 months of combined androgen blockade, respectively [99,100]. Since we already had obtained evidence for the high efficacy of long term and continuous CAB in localized prostate cancer [101], it was felt important to examine the long term outcome of these patients as assessed by biochemical failure or PSA rise following cessation of continuous CAB previously

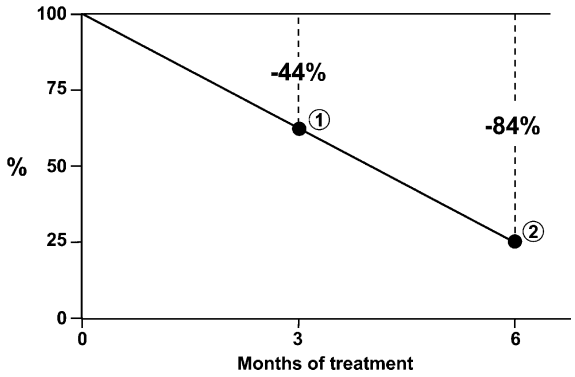

Fig. 8. Inhibitory effect of 3- and 6-months of treatment with the combination of an LHRH agonist and flutamide (250 mg, three times a day) on the volume of the cancer measured on the radical protatectomy specimens [99,100].

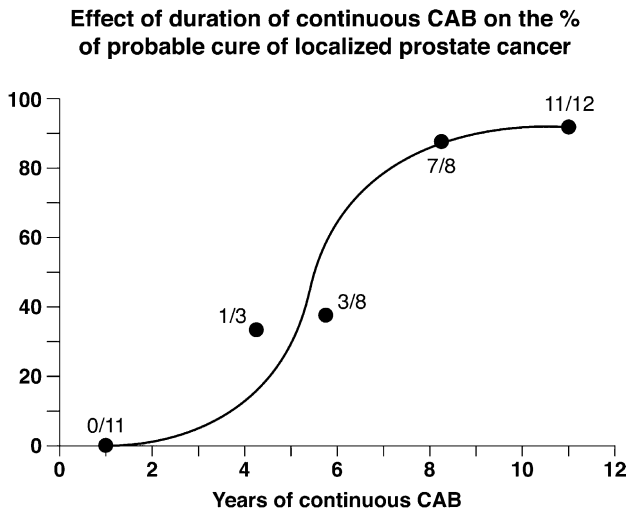

Fig. 9. Effect of duration of treatment of localized prostate cancer with continuous CAB on the probability of long term control or "cure of the disease" illustrated by no recurrence of PSA rise for at least 5 years after cessation of CAB. The point at 4.75 years of treatment (33%) refers to the three patients treated with CAB for 3.5–5.0 years and followed for at least 5 years, while the point at 5.75 years refers to the eight patients treated continuously with CAB for 5.0–6.5 years before cessation of treatment. The point at 8.25 years refers to the eight patients treated continuously for 6.5–9.0 years while the point at 11 years refers to the 13 patients treated for 10–1.7 years with continuous CAB before stopping treatment. All patients were followed for at least 5 years after cessation of continuous CAB or until PSA rise. Only one patient has died from prostate cancer while 18 have died from other causes [64].

administered for periods up to 11.3 years. The effect of CAB on long-term control or possible cure of prostate cancer was thus evaluated by the absence of biochemical failure or the absence of PSA rise for at least 5 years after cessation of continuous treatment. A total of 57 patients with localized or locally advanced disease received CAB for periods ranging from 1 to 11 years. With a minimum of 5 years of follow-up after cessation of long-term CAB, only two PSA rises occurred among 20 patients with Stage T2–T3 cancer who stopped treatment after continuous CAB for more than 6.5 years, for a nonfailure rate of 90% (Fig. 9). On the other hand, for the 11 patients who had received CAB for 3.5–6.5 years, the nonfailure rate was only 36%. The serum PSA increased within 1 year in all 11 patients with Stage B2/T2 treated with CAB for only 1 year, thus indicating that active cancer remained present after short-term androgen blockade despite undetectable PSA levels. Most importantly, in all patients who had biochemical failure after stopping CAB, serum PSA rapidly decreased again to undetectable levels when CAB was restarted, PSA remaining at such low levels afterward. Of these patients, only one patient had died of prostate cancer at last follow-up [64].

These are remarkable results obtained in patients with localized prostate cancer. Treatment, however, must be continuous, non interrupted and should last for many years. An important observation made is that in the patients where PSA increases for a second time following cessation of treatment, administration of combined androgen blockade was successful in all cases in decreasing PSA to undetectable levels again, thus showing that even after a long duration of treatment, resistance to androgen blockade had not developed.

The present results obtained in prostate cancer patients diagnosed with localized prostate cancer and treated continuously for many years with combined androgen blockade are not too different from the results that we have recently obtained with human breast tumors in nude mice where complete estrogen blockade led to the disappearance or cure of the tumors in 61% of cases within a few months [102]. In fact, in both breast and prostate cancer, when the estrogens in breast cancer and the androgens in prostate cancer are blocked optimally, cure of the disease can be achieved with hormonal therapy.

The success of treatment, however, takes a long time before complete apoptosis or total cell death is achieved. Breast and prostate cancers have many characteristics in common and much can be learned from looking at the results obtained in each of them. In fact, when we examine the biology of these two diseases, there are many common features, specially the high level of sensitivity to hormones. Such results clearly indicate that intermittent androgen blockade should remain experimental and should not be used outside clinical trials.

With the knowledge of the above-described data, it seems reasonable to suggest that the minimal duration of continuous CAB in localized prostate cancer should be 6 years, thus providing an approximately 50% probability of long-term or possible cure of the cancer. With longer duration of CAB, the probability increases to about 90% at 8–10 years of treatment. The present data indicate that possible cure of the disease can be obtained in the majority of patients with localized prostate cancer treated continuously with CAB for more than 6 years, thus raising hopes for the successful treatment of patients who fail after surgery, radiotherapy or brachytherapy where no or minimally effective alternative therapeutic approach exists. Such data clearly indicate the interest of a large scale randomized study comparing monotherapy versus CAB in the group of patients showing biochemical failure after first

therapy with a curative intent. Care should be taken, however, to start treatment early after the rise of serum PSA in order to use androgen blockade at its maximal level of efficacy, namely when the cancer is still localized to the prostate or the prostatic area, before metastases reach the bones when cure becomes an exception.

While its efficacy, especially in localized disease, is well recognized [64,88–99,101,103], androgen blockade is accompanied by hot flushes, loss of libido and sexual potency, as well as bone loss and potentially osteoporosis [104–106].

10. Conclusion: death from prostate cancer can already be an exception

While showing the particularly high efficacy of hormonal therapy in localized prostate cancer, the present data clearly indicate that long-term treatment somewhat similar to the 5 years of Tamoxifen in breast cancer, is required for optimal control of prostate cancer. Great caution should be taken, however, about the interpretation of serum PSA that must be used as surrogate marker. In fact, serum PSA rapidly and easily decreases to undetectable levels under androgen blockade although the cancer remains present for much longer periods of time, usually for at least years as demonstrated in our recent study [64]. For this reason, intermittent therapy should not be recommended outside prospective and randomized clinical trials.

When prostate cancer is diagnosed, it is organ-confined in about 40 to 50% of cases. The choice of therapy is then surgery, radiotherapy, brachytherapy or combined androgen blockade alone or in combination with surgery, radiotherapy or brachytherapy. It is important to visualize (Fig. 10) that prostate cancer takes a long time to develop before it can be detectable by serum PSA, digital rectal examination and/or transrectal ultrasonography of the prostate. However, there is a small window of time during which the cancer can be detected at a stage when it is still curable by the available approaches. It does not take very long, usually, two, three, four or at most five years, before the cancer migrates to the bones and then becomes non curable. If the window of curability of prostate cancer is missed, one faces major problems and the cancer becomes practically impossible to cure. At the advanced stage, the best that can be done is to prolong life (Fig. 6).

It is very important to remember again that contrary to what can be found in most textbooks, orchiectomy or treatment with LHRH agonists does not reduce exposure of the

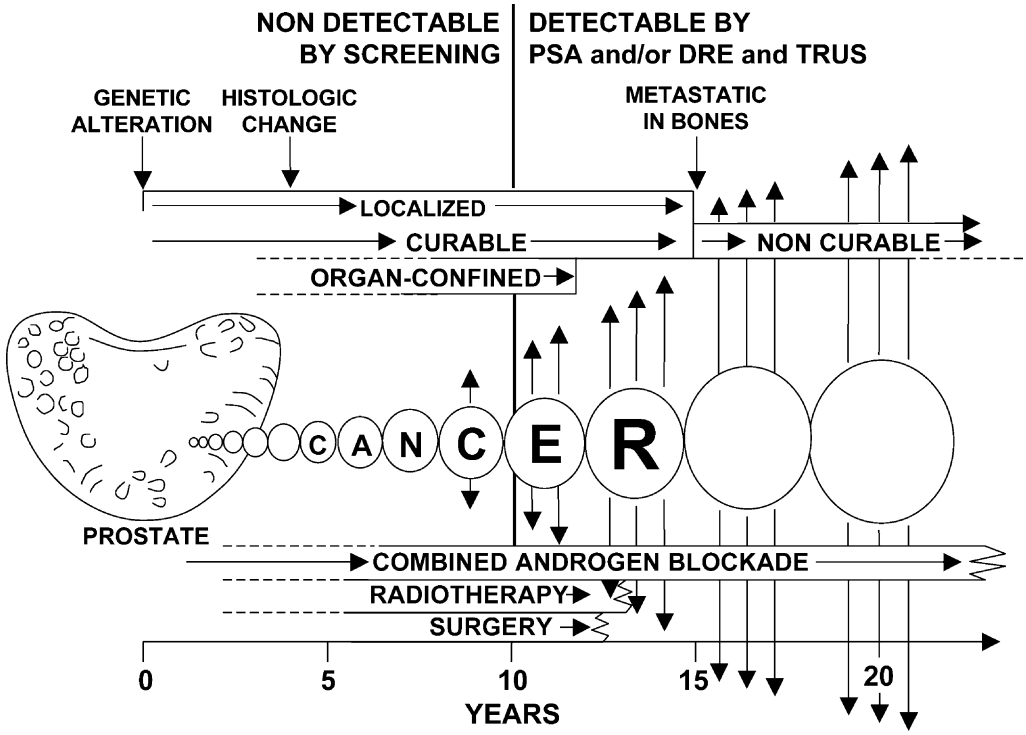

Fig. 10. Schematic representation of the evolution of prostate cancer from appearance of the first genetic change, which, following other mutations, will lead to a cancer cell. For years, the cancer cells can be seen by histology or gene markers but it is only when the tumor reaches a relatively large volume (0.3 cc) that diagnosis can be made by screening using prostate specific antigen (PSA), digital rectal examination, and transrectal echography of the prostate. At that stage of possible diagnosis by screening, approximately 50% of the cancers have already migrated outside the prostate and are not organ-confined. Radical prostatectomy can cure the disease when the cancer is organ-confined. Radiotherapy and brachytherapy (seed implants) are believed to have about equal efficacy. Combined androgen blockade can also cure the disease if treatment is started before the cancer migrates to the bones. At the advanced stage of bone metastasis, only combined androgen blockade is active against the disease and can prolong life compared to monotherapy, although the possibility of a cure is minimal. Much remains to be understood about the treatment of localized disease, but this diagram is drawn according to the best knowledge available today [64].

tissues to androgens by 90–95%. In fact, removal of testicular androgens decreases DHT levels in the prostate by only 50–60%, thus leaving an important amount of androgens free to continue to stimulate prostate cancer. Most importantly, the presence of a significant concentration of androgens leaves the cancer exposed to additional mutations and the development of resistance to androgens and to hormonal therapy. In practical terms, and based upon our today's best knowledge of the endocrinology of the prostate, the only reasonable hormonal treatment for prostate cancer is the combined use of an LHRH agonist or orchiectomy in association with a pure antiandrogen, namely flutamide, nilutamide or bicalutamide (150 mg or more daily).

With the antiandrogens presently available, the potency is too low in order to be able to use them alone. In fact, the use of bicalutamide alone (150 mg daily) results in a blockade of androgens comparable to orchiectomy, thus leaving approximately 50% of androgens free to stimulate prostatic cancer growth. In the future, with the availability of more potent antiandrogens, it should be possible to use an antiandrogen alone in the treatment of prostate cancer. In fact, when comparing with the available antiestrogens, namely Tamoxifen or Raloxifene, these compounds are at least 300 times more potent than the available antiandrogens in terms of affinity for the steroid receptor. There is thus a long way to go before antiandrogens alone can be used and block the androgen receptor sufficiently to expect optimal results or results comparable to those achieved by combined androgen blockade.

It is important to remember that when the cancer is localized to the prostate or in the area close to the prostate, the cancer remains highly sensitive to androgen blockade. However, if we do not act rapidly and the cancer reaches the bones, the treatment becomes of much reduced efficacy. With the present knowledge, it is thus clear that all available means should be taken to diagnose prostate cancer early and to use efficient therapy immediately in order to prevent prostate cancer from migrating to the bones where treatment becomes extremely difficult and cure or even long-term control of the disease is an exception. The only means of preventing prostate cancer from migrating to the bones and becoming incurable is efficient treatment at the localized stage of the disease. In fact, since radical prostatectomy, radiotherapy and brachytherapy (implantation of radioactive seeds in the prostate) can achieve cure in about 50% of cases, these approaches are all equally valid choices as first treatment of localized prostate cancer. Androgen blockade should also be considered as first line treatment. The most important, however, is to follow closely serum PSA after surgery, radiotherapy and brachytherapy and to start CAB as soon as the first sign of recurrence of the cancer appears. It is also clear from the data summarized above that CAB alone could well be the most efficient therapy of localized prostate cancer while it has already been recognized as the best therapy for metastatic disease.

The first discovery in this area was that of Huggins and his collaborators in 1941 who observed the benefits of orchiectomy or high doses of estrogens in advanced prostate cancer and then concluded to the high sensitivity of prostate cancer

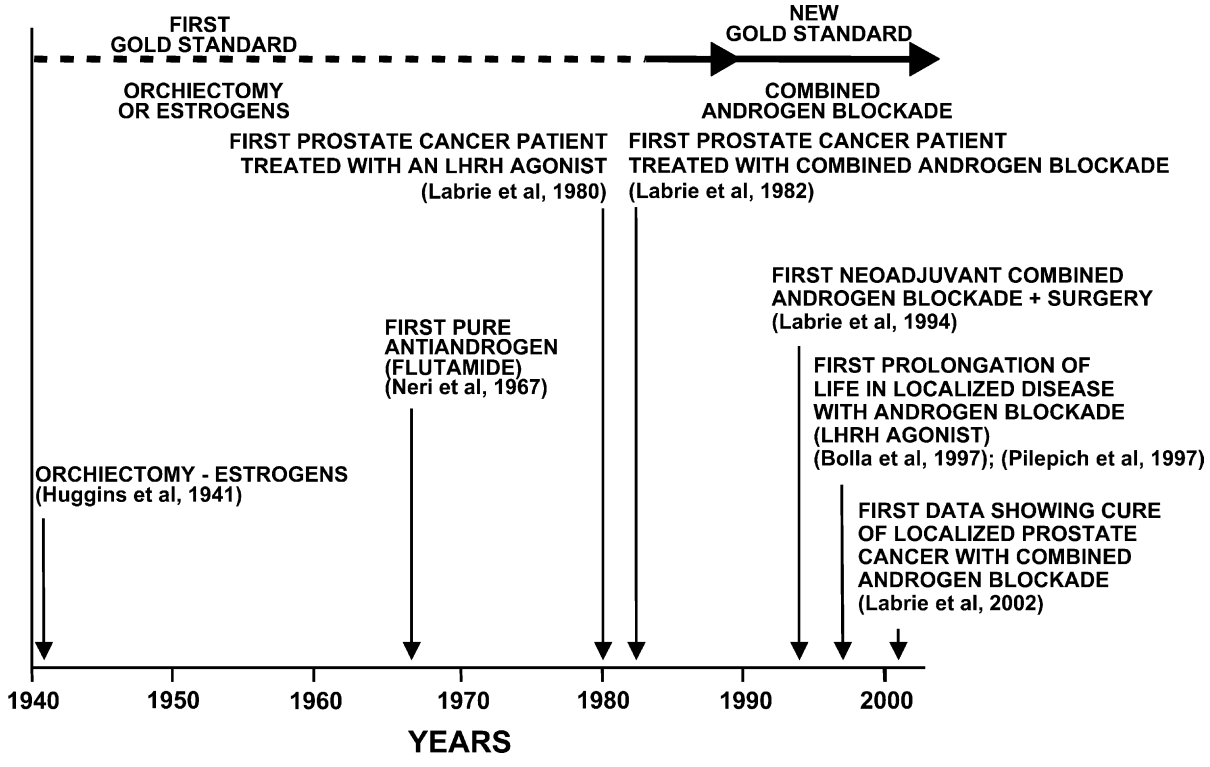

Fig. 11. Landmarks in the development of hormonal therapy of prostate cancer.

to androgens. This treatment has been used continuously until 1980 when we discovered at the Laval University Medical Center in Québec City that LHRH agonists could achieve medical castration without the side effects of estrogens and the psychological limitations of orchiectomy (Fig. 11). Two years later, we found that approximately 50% of androgens were left in the prostate following medical or surgical castration, thus leading to the discovery of the important role of adrenal DHEA as source of the androgens synthesized locally in the prostate as well as in a long series of peripheral target tissues.

Based upon this observation, we then developed combined androgen blockade whereby the androgens of both testicular and adrenal origins were blocked simultaneously at start of treatment with the combination of an LHRH agonist and a pure antiandrogen. This has led to the first treatment shown to prolong life in prostate cancer (Fig. 10). The first prolongation of life in localized disease, on the other hand, was achieved in 1997 by Bolla et al., and Pilepich et al. when the combination of radiotherapy and androgen blockade was found to be superior to radiotherapy alone. Then, in 2002, we have made the observation that combined androgen blockade alone administered continuously for 6.5 years or more leads to a cure of the disease in 90% of cases, thus suggesting that androgen blockade could well be the most efficient treatment of localized prostate cancer.

Such data suggest that androgen blockade should be considered as an alternative for the treatment of localized disease, while, at the metastatic stage, it is the only efficient therapy available. To the best of our knowledge, screening can be performed easily and successfully at a low cost, thus permitting the diagnosis of prostate cancer at a localized stage in almost all cases (99%). Then, using the approaches which are available, namely surgery, radiotherapy, brachytherapy and androgen blockade administered at the right dose and at the right time, men should not die from prostate cancer anymore.

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