

Combined androgen blockade and treatment of localized prostate cancer: a real hope when approaching the year 2000

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Introduction

Although much remains to be accomplished, the attitude towards prostate cancer has improved significantly over the recent years. The worst case attitude is that prostate cancer is not a serious problem, since it usually affects men in their 60s and 70s, at an age where other causes of death become frequent. This lack of interest derives from the erroneous impression that prostate cancer grows so slowly that other causes of death will usually occur before prostate cancer can lead to death. However, the fact that prostate cancer is the second cause of death in men certainly casts serious doubts about such thinking. Moreover, the observation that more than 70% of deaths from prostate cancer occur after the age of 70 years is not a valid reason not to exert our best efforts to avoid, as much as possible, the particularly serious suffering associated with prostate cancer death.

The two most important scientific facts which should be used as basis for a successful fight against prostate cancer are: the androgens acting in the prostate originate from two sources of approximately equal importance, namely the testicles and the adrenals, thus indicating the need for combined androgen blockade (CAB); the efficacy of androgen deprivation is almost certainly greater for localized than for metastatic disease, thus indicating the critical importance of early treatment.

As a general observation, it should be mentioned that androgen blockade is the only treatment for prostate cancer shown in randomized clinical trials to prolong life by an average of 3 months and, most importantly, this success has now been achieved at both the localized and advanced stages of the disease (Labrie *et al.* 1982, Béland *et al.* 1988, Crawford *et al.* 1989, Denis *et al.* 1993, Janknegt *et al.* 1993, Bolla *et al.* 1997, Denis *et al.* 1998). Such data provide good reasons to believe that androgen blockade, in addition to remaining the first-line treatment of advanced disease, should now be considered as an even

more efficient treatment of early stage disease; endocrine therapy could thus be part of the therapeutic plan of any patient treated for prostate cancer at any stage of the disease.

Endocrinology of prostate cancer intracrinology

Following the observations of Huggins and his colleagues (1941), the next most important advance in our understanding of the endocrinology of prostate cancer 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. 1). In fact, plasma DHEA-S levels in adult men are 100 to 500 times higher than those of testosterone (Labrie *et al.* 1985), thus providing high levels of the substrate required for conversion into androgens in the prostate as well as other peripheral intracrine tissues.

Although orchiectomy, estrogens, or LHRH agonists or antagonists (through blockade of release of bioactive LH) cause a 90-95% reduction in testosterone concentration in the circulation (Labrie *et al.* 1980, 1985 Waxman *et al.* 1983), a much smaller effect is seen on the only parameter directly reflecting androgenic action, namely the intraprostatic concentration of the potent androgen, DHT. In fact, intraprostatic DHT levels are reduced by only 50 to 70% following medical or surgical castration (Labrie *et al.* 1985, Bélanger *et al.* 1986).

Added to the androgens of testicular origin, 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. Contrary to the previous

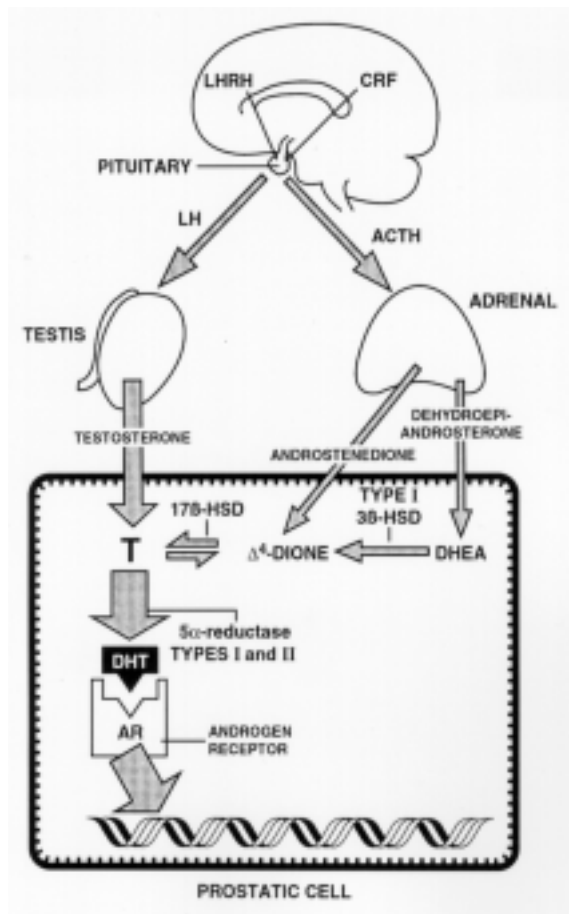


Figure 1 Intracrine activity in the human prostate or bio-synthetic steps involved in the formation of the active androgen, dihydrotestosterone (DHT), from testicular testosterone as well as from the adrenal precursors dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), and androstenedione (4-dione) in human prostatic tissue. 17 β -HSD=17 β -hydroxysteroid dehydrogenase; 3 β -HSD=3 β -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: approximately 60% of total intraprostatic DHT originates from the testes, while 40% is from adrenal origin in a 65-year-old man. The testis secretes testosterone (T) which is transformed into the more potent androgen DHT by 5 α -reductase in the prostate. Instead of secreting T or DHT directly, the adrenal secretes very large amounts of precursors of DHT, namely DHEA and DHEA-S as well as some androstenedione (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, by inactive activity. In fact, the enzymatic complexes DHEA sulfatase, 3 β -HSD, 17 β -HSD and 5 α -reductase are all present in the prostatic cells, thus providing 40% of total DHT in this tissue.

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 androgens, testosterone and DHT. In fact, the prostate synthesizes its own androgens to a level comparable to that of the androgens of testicular origin.

Knowledge in this area has recently made rapid progress, with the elucidation of the structure of most of the tissue-specific cDNAs and genes that encode the steroidogenic enzymes responsible for the transformation of DHEA-S and DHEA into androgens and/or estrogens in peripheral tissues (Andersson & Russel 1990, Andersson *et al.* 1991, Labrie *et al.* 1992b,c, 1995a,c, 1996d, 1997b, Rhéaume *et al.* 1992, Bernier *et al.* 1994a,b, Luu-The *et al.* 1995a,b).

Combined androgen blockade

Metastatic disease

As indicated above, the discovery that the adrenals contribute 30-50% of total androgens in the human prostate (Labrie *et al.* 1985, 1993a) through local transformation of DHEA of adrenal origin into the potent androgen, DHT (Labrie 1991, Labrie *et al.* 1993a,c, 1996d, 1997b) clearly indicates that androgen blockade should be a two-way approach that includes: (1) elimination of testicular androgens by orchiectomy (Huggins & Hodges 1941) or an LHRH agonist (Labrie *et al.* 1980, Faure *et al.* 1982) combined, at start of treatment, with (2) blockade of the action of DHT made locally in the prostate cancer using a pure antiandrogen, such as flutamide (Eulexin) or one of its derivatives, namely nilutamide (Nilandron) or bicalutamide (Casodex) at the appropriate dose.

Although 50-60% of androgens can be eliminated by orchiectomy or medical castration with an LHRH agonist, the best method available for interfering with the action of androgens produced locally in the prostate is the use of a pure antiandrogen, which prevents the interaction of testosterone and DHT with the androgen receptor (Labrie 1993, Labrie *et al.* 1996a,c). A pure antiandrogen should be a compound that has a high specificity and affinity for the androgen receptor without any androgenic, estrogenic, progestational, glucocorticoid, or other hormonal or antihormonal activity (Labrie 1993, Labrie *et al.* 1996c). To date, only flutamide (Neri *et al.* 1967, Katchen & Buxbaum 1975, Simard *et al.* 1986) and its analogues, nilutamide (Moguilewsky *et al.* 1986) and bicalutamide (Furr *et al.* 1987), are available as pure antiandrogens for clinical use.

morbidity. The excellent local control obtained in the present study is in agreement with our previous data showing that, in 17 patients with low urinary tract obstruction, such androgen blockade alone relieved the obstruction in 16 of 17 patients and only one patient relapsed locally during the course of the study (Emond *et al.* 1989).

Since no prospective randomized study has been performed, comparison with the large series available is thus the only possible way of evaluating the relative efficacy of the present approach. Accordingly, following the 'Consensus statement in the management of clinically localized prostate cancer' of the National Institute of Health (1987), which reviewed data from studies with reasonably large numbers of patients, one can conclude that the results of the most widely accepted therapeutic alternative for T₃ prostate cancer, namely radiation therapy, indicate an overall survival of 64% at five years and 35% at ten years while, in our study, the five year-survival is 74.2% and 53.3% at 10 years. Moreover, the 74.2% survival at 5 years in the present study compares favorably with the 62% survival achieved with radiotherapy alone in a similar group of patients (Bolla *et al.* 1997). The benefits of long-term CAB observed in our series of stages C/T₃ patients is even more encouraging when one realizes that 40% of our subjects had elevated PAP serum values at diagnosis. This feature suggests that our patients were more likely to have disseminated disease at diagnosis (Paulson 1980), thus removing surgery and radiation therapy as alternatives.

Combined androgen blockade and localized disease

Introduction

Despite progress in the treatment of advanced or metastatic prostate cancer (Labrie *et al.* 1982, Crawford *et al.* 1989, Denis *et al.* 1993, 1998, Janknegt *et al.* 1993, Caubet *et al.* 1997, Dijkman *et al.* 1997), it is well recognized that the only possibility of a significant reduction in prostate cancer death is treatment of localized disease. It is reasonable to assume that the recently observed decrease in deaths from prostate cancer (Hoeksema & Law 1996) is due to earlier diagnosis with serum PSA (Killian *et al.* 1986, Labrie *et al.* 1992a, 1996b) and transrectal echography of the prostate (Lee *et al.* 1989), coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy and endocrine therapy (Cooner *et al.* 1990, Hanks *et al.* 1991, Labrie *et al.* 1994, Pilepich *et al.* 1995, Blasko *et al.* 1996, Bolla *et al.* 1997, Laverdiere *et al.* 1997).

Choice of treatment of localized disease

Despite the fact that clinically localized prostate cancer has become the predominant stage at diagnosis, there is no randomized and prospective comparison of the efficacy of the available treatments (Consensus Conference 1987, Middleton *et al.* 1995). The only exception is the recent and most important demonstration that the addition of androgen blockade to radiotherapy prolongs disease-free survival and overall survival compared with radiotherapy alone in stage T₃ patients (Bolla *et al.* 1997). This is the first demonstration that treatment can prolong life in localized prostate cancer and these important benefits have been achieved with androgen blockade.

The lack of sufficient scientific information makes difficult the choice of treatment for localized disease. However, based upon the most rigorous evaluation of the data available in the literature and our own experience, we will make the suggestions which, in our opinion, provide the best chance of controlling the cancer while minimizing the risk of progression to metastatic disease and the resulting death from prostate cancer. The complications associated with radical prostatectomy, radiation therapy and brachytherapy should also be taken into account in the

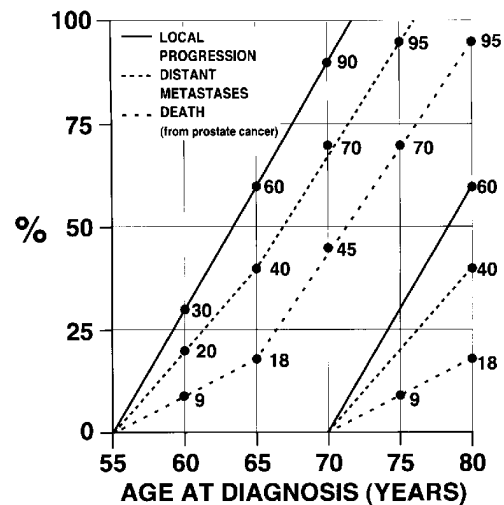


Figure 3 Estimate of progression (...), distant metastasis (--), and death (-) rates in patients diagnosed as having localized prostate cancer at the ages of 70 and 55 years, respectively. Disease-specific death, distant metastases and local progression have been estimated at 18, 40 and 60, respectively, at 10 years of follow-up (Moskovitz *et al.* 1987, Lerner *et al.* 1991, Whitmore Jr *et al.* 1991, Chodak *et al.* 1994, Aus *et al.* 1995) for patients diagnosed at the age of 70 years. Similar estimates have been made for patients diagnosed at the age of 55 years. For these patients, the risks of local progression, distant metastases and death from prostate cancer are estimated at 100, 95 and 70%, respectively, during the following 20 years.

choice made by the patient (Middleton *et al.* 1995). The most frequently reported complications are incontinence, impotence (erectile dysfunction), cystitis, rectal injury, bleeding as well as bladder neck and urethral stricture (Middleton *et al.* 1995).

The treatment options for localized disease are radical prostatectomy, external beam radiotherapy, brachytherapy and hormone therapy alone, a combination of hormone therapy with surgery, radiotherapy, brachytherapy or even deferred treatment (watchful waiting). Life expectancy, rather than the age of the patient should be the factor considered in treatment selection.

For a series of reasons previously described (Gann *et al.* 1995, Hugosson *et al.* 1995, Labrie 1995, Labrie *et al.* 1995b), watchful waiting is not, for almost all patients, an alternative to be considered, except in patients with a short life expectancy. The real problem with watchful waiting is that all cancers progress, albeit at a different rate, and will kill the patient if he lives long enough. As illustrated in Fig. 3, the best estimates of the probability of local progression, metastases (not curable), and death for a 70-year-old man during the next 10 years are 60%, 40%, and 18%, respectively (Labrie *et al.* 1995b). For a 55-year-old man, the risks of local progression, distant metastases, and death from prostate cancer are 90%, 70%, and 45%, respectively, if he lives up to the age of 70 years. The curves illustrated in Fig. 3 for a 55-year-old patient can be moved along the abscissa for any age at diagnosis in order to estimate, for each patient, the risk of serious complications (including cancer death) if the clinically localized prostate cancer is not treated immediately at diagnosis.

This high risk of complications and even cancer death in patients diagnosed with localized prostate cancer and who do not receive immediate treatment is due to the fact that approximately 50% of cancers are already outside the prostate at the time of diagnosis (Labrie *et al.* 1994, O'Dowd *et al.* 1997). Moreover, as mentioned above, approximately 20% of the patients having organ-confined disease when the prostate is surgically removed will show failure within 10 years. Taking into account the fact that the curative therapies will eliminate cancer only in patients having disease confined to the prostate, only 40% of the men diagnosed with localized prostate cancer are expected to be cured by surgery, radiotherapy or brachytherapy alone. The consequence is that 60% of men need systemic therapy in addition to local treatment. Another major but related problem is that one cannot distinguish with certainty which men diagnosed with localized prostate cancer have truly organ-confined disease (40%) from those who already have disseminated disease (60% of them).

High efficacy of combined androgen blockade alone in localized disease

It is pertinent to indicate that CAB alone is highly efficient in keeping localized prostate cancer under control. In a personal series of 26 stage T₂-T₃ patients who received flutamide and an LHRH agonist for up to 12 years (median, 7.1 years), a rise in PSA occurred in only one patient after 8 years and 4 months of treatment (Labrie *et al.* 1997a).

The side effects of CAB are well tolerated, namely hot flushes usually lasting for a few months at start of therapy, impotence, and loss of libido (Labrie *et al.* 1985, Crawford *et al.* 1989, Denis *et al.* 1993). Unlike estrogens, the combination of flutamide and a LHRH agonist leads to an improved lipid profile compared with orchiectomy (Moorjani *et al.* 1988).

The present data clearly indicate that androgen deprivation is extremely efficient for the treatment of clinically localized prostate cancer, its ability to control the disease in 26 patients for up to 8.3 years being possibly superior to that of radical prostatectomy and radiation therapy alone (Fig. 4). Although a 15 year follow-up is required to assess the long-term effect of treatment of localized prostate cancer, it is recognized that local recurrence and especially serum PSA can be used as an interim parameter to evaluate efficacy (Zietman *et al.* 1994b). Without a randomized study, however, it is not possible to strictly compare one clinical series with another. Despite these limitations, it is of interest to see in Fig. 4 that the 5-year actuarial rate of recurrence in a similar category of patients who had radical prostatectomy was 24% at the Johns Hopkins Hospital (Morton *et al.* 1991), while it was 57% at the Boston University Medical Center (Zietman *et al.* 1994a) and 31% in a comparable series at the UCLA Medical Center (Trapasso *et al.* 1994). In a series of stage T₁₋₂ prostate cancer at the Cleveland Clinic Foundation, the 5-year recurrence rate was calculated at 39% (Kupelian *et al.* 1996). Similarly, PSA failure after radiation therapy has identified a high level of cancer recurrence. Thus, following radical irradiation for T₁ and T₂ disease, the 4-year% actuarial rate of recurrence has been reported as 35% at the Boston University Hospital (Zietman *et al.* 1994b) and 59% at Baylor University (Goad *et al.* 1993). A 5-year recurrence rate of disease-free survival has been calculated at 40% at the MD Anderson Hospital (Zagars & von Eschenbach 1993, Labrie *et al.* 1997a).

Since serum PSA had remained undetectable up to a treatment duration of 11.8 years (median: 7.1 years) in all other 25 patients, treatment has been stopped in 17 patients of this group. These 17 patients have now been followed for a median duration of 2.0 years. As can be seen in Fig. 5A, only three patients have shown progression of serum

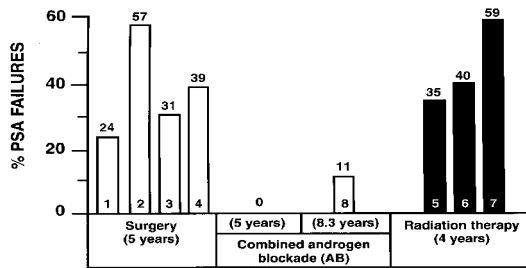


Figure 4 Comparison of the failure rate after combined androgen blockade (first failure at 8.3 years in this study versus failure rates of 24%, 57%, 31% and 39% at 5 years after radical prostatectomy and 35%, 40%, and 59% 4 years after the start of radiation therapy. (1- (Morton *et al.* 1991); 2- (Zietman *et al.* 1994a); 3- (Trapasso *et al.* 1994); 4- (Kupelian *et al.* 1996); 5- (Zietman *et al.* 1994b); 6- (Kaplan *et al.* 1993); 7- (Goad *et al.* 1993); 8- (Labrie *et al.* 1997a)).

PSA. Including the median posttreatment follow-up of 2.4 years (up to 4.2 years) in the 17 patients who stopped CAB, median overall follow-up is 8.9 years, ranging from 2.8 to 14.1 years. One patient died at 8.4 years from a noncancer related cause. When treatment is restarted in such patients, it is usual for the PSA to return to undetectable levels.

Figure 6 shows the dramatic effect of the duration of CAB on the PSA failure rate after cessation of endocrine therapy. Where treatment had been given for one year only in a series of T₂ patients, the serum PSA did not remain undetectable for one year in any of the 11 patients. However, in 14 of 17 patients with category T₂ disease treated for 7 years and 22 of 26 patients with T₃ disease, treated for 10 years the PSA remained undetectable for 2.4 and 1.8 years of follow-up.

Such data obtained with CAB alone are superior to those obtained in comparable groups of patients treated by surgery or radiotherapy alone (Fig. 4). Moreover, when CAB was stopped in 44 stage T₂-T₄ patients treated for a median duration of 8-10 years, a PSA rise was seen in only 6 of them (14%) during a two-year follow-up period. Most importantly, PSA then returned to undetectable levels in all patients when CAB was reinstated. On the other hand, when CAB was stopped in 11 T₂ patients treated for only 1 year, a PSA rise was observed in all patients within 1 year after cessation of treatment, thus indicating the need for androgen blockade of much longer duration than one year.

Such data, combined with those of the 3-year treatment period of Bolla *et al.* (1997) and the results obtained following 10.5 months versus 3 months of CAB

associated with radiotherapy (Laverdiere *et al.* 1997) as well as the benefits of 5 years of Tamoxifen as adjuvant to surgery in breast cancer compared with 2 years (Swedish Breast Cancer Cooperative Group 1996), indicate the importance of administering CAB as neoadjuvant (before surgery or radiation therapy) and/or adjuvant for a continuous period of a few years, probably five years (Labrie *et al.* 1997a). In agreement with these findings, randomized and prospective international studies comparing an LHRH agonist and flutamide (CAB) associated with prostatectomy, radiation therapy or brachytherapy performed at 6 months followed by continuation of CAB for 4.5 additional years compared with CAB alone for 5 years are now opened for accrual in Canada. Based upon the above-summarized data, we estimate that a total period of 5 years of CAB is the best choice for the duration of androgen blockade.

Combined androgen blockade alone or in association with surgery or radiotherapy

In men unable to receive curative therapy or having a less than 10-year life expectancy, combined androgen blockade alone appears as a highly efficient means of controlling localized prostate cancer.

Based upon the most encouraging data obtained in patients with stage T₂ disease (Labrie *et al.* 1997a), CAB alone is a valid alternative, especially for patients aged 70 years or more and for those having a life expectancy of less than 10 years.

For younger men having a more than 10-year life expectancy, the best approach, however, is likely to be the association of long-term combination therapy (probably 5 years) with surgery, radiotherapy or brachytherapy.

Our own belief, based upon the data summarized above, is, for young patients, to use CAB for 6 months before surgery and to continue CAB after surgery for a total of 5 years following cessation of CAB. A rise of PSA above 0.2 ng/ml should be a signal to immediately reinstitute CAB for 3 years. For patients having the best prognosis, radical prostatectomy alone can be performed with serum PSA measured every 2 months as follow-up. At first PSA rise above 0.2 ng/ml (Hybritech assay or its equivalent), CAB should be started without interruption for 5 years.

With the information summarized above and the recent demonstration that androgen blockade for 3 years combined with radiation therapy leads to a 45% improved survival at 5 years compared with radiation therapy alone (Bolla *et al.* 1997), it seems logical to recommend the association of CAB for 5 years when radiation therapy is used, at least in stage T₃ patients. In fact, the 45% overall survival advantage obtained by adding 5 years of androgen blockade to radiotherapy was in clinical stage T₃

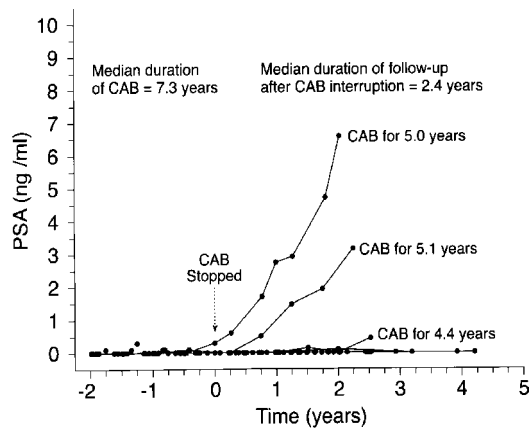


Figure 5 Change in serum PSA after cessation of combined androgen blockade (LHRH agonist+Flutamide) (CAB). Panel shows seventeen patients with stage T₂ disease, who received CAB for a median of 7.2 years. Serum PSA increased in only 3 patients during median follow-up of 2.2 years.

disease (Bolla *et al.* 1997). However, as mentioned above, since approximately 60% of clinical stage T₂ cancers are in fact pathological stages T₃ or even T₄ cancers, it would appear reasonable to apply the same strategy of CAB to external beam radiation therapy for both stages T₂ and T₃ disease.

For stages T₁-T₂ disease, one possibility is to perform radiotherapy or brachytherapy first after 6 months of CAB and then start CAB for 5 years only if PSA rises. Serum PSA should be measured every 2 months. An increase of serum PSA of 0.5 ng/ml within 12 months or an increase above 1.0 ng/ml should be the signal to reinstitute CAB for 3 years followed by the same follow-up of serum PSA measurement every second month.

Because the aim of androgen blockade is to cause a maximal reduction in prostatic androgen levels in order to induce maximal atrophy, apoptosis, and death of prostate cancer cells, combined androgen blockade using a pure antiandrogen (Labrie *et al.* 1982, Labrie *et al.* 1985) in association with an LHRH agonist or surgical castration is the most logical approach.

Summary and conclusions

The present data show that an optimal use of the available diagnostic and therapeutic approaches can have a major impact on quality of life and survival in prostate cancer. The only way to have a major impact on prostate cancer death is clearly treatment of localized disease. Moreover, it has become clear that, in analogy with breast cancer where significant survival benefits were obtained only after 2-5 years of adjuvant Tamoxifen therapy, combined

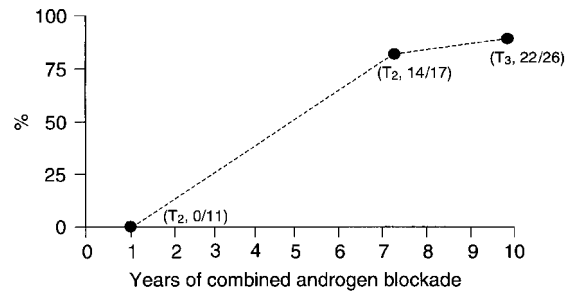


Figure 6 Percentage of patients where serum PSA remains undetectable following cessation of treatment in 55 stage T₂ or T₃ prostate cancer patients who received combined androgen blockade for median durations of 1 year (0/11 T₂ patients), 7.1 years (82.4%; 17 T₂) or 9.9 years (84.6%; 26 T₃) (Labrie *et al.* 1997a).

androgen blockade must be administered for much longer periods than done so far, most likely up to 5 years.

Although PSA shows unique usefulness as an early sign of recurrence of cancer after any form of therapy, its high sensitivity to androgen deprivation needs caution. In fact, serum PSA decreases to undetectable levels much before generalized apoptosis or control of cancer proliferation is achieved. In other words, an undetectable serum PSA is not equivalent to cancer cell death. It should be remembered that the only form of endocrine therapy demonstrated to prolong life is the one where androgen blockade was administered continuously for years without interruption. Before being recommended, intermittent therapy needs to be proven in large randomized trials as being equivalent to continuous treatment on survival, the prime and essential objective of prostate cancer therapy. It is pertinent to remember that continuous androgen blockade is the only treatment shown to prolong life in both metastatic and localized disease.

The important benefits of androgen blockade in localized prostate cancer are in agreement with the well known observation that, in patients with metastatic disease treated with CAB, progression occurs almost always in the bones and not in the prostate, thus clearly indicating that prostate cancer localized to the prostatic area is highly sensitive to androgen deprivation. All available means should be taken 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 no longer possible.

A major source of controversy concerning early diagnosis and treatment of prostate cancer is that, until recently, no prospective and randomized trial had shown statistically significant benefits of treatment of localized prostate cancer on survival (Kolata 1987). The absence of data from well designed clinical trials was erroneously interpreted as negative data. Most fortunately, two

prospective randomized trials have recently demonstrated for the first time that not only quality of life but, most importantly, prolongation of life could be achieved in localized prostate cancer patients treated with androgen blockade. In the EORTC trial performed in stage T₃ patients, survival at 5 years was increased from 62% in the group of patients who received radiation therapy alone to 79% (45% difference) in those who received androgen blockade using an LHRH agonist for 3 years and an antiandrogen for one month in association with radiotherapy (Bolla *et al.* 1997). A similar observation has been made in RTOG trial 08351 in the subgroup of high Gleason score patients (Pilepich *et al.* 1997). No valid reason remains to doubt that treatment of clinically localized prostate cancer can prolong survival.

In addition to the major impact on prostate cancer deaths, the economic savings on health care costs has been previously discussed (Labrie *et al.* 1993*b,d*, Littrup *et al.* 1994, Aus *et al.* 1995). The calculations performed leave little doubt that the strategy based upon efficient screening and treatment, namely androgen blockade, surgery, radiotherapy or brachy-therapy alone or in combination with androgen blockade should play a key role in the successful fight against prostate cancer while decreasing the costs for the health care system and society (Labrie 1994, Labrie *et al.* 1995*b*).

Major progress has been made by many groups during the last decade in the field of early diagnosis and early treatment (surgery, radiotherapy, brachytherapy, and hormone therapy) of prostate cancer while our understanding of the endocrinology of this disease has also made significant progress, including the most important demonstration that androgen blockade prolongs life in both localized and advanced prostate cancer. There is no doubt, however, that only a concerted effort of urology, endocrinology, radiation therapy, and many other specialties can set the stage for the most successful fight against this most devastating disease. The significant progress made, however, is a stimulus to move forward at an even more accelerated pace.

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