

# Androgen blockade in prostate cancer in 2002: major benefits on survival in localized disease

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## Abstract

The last 20 years have witnessed major advances in the field of prostate cancer, both in terms of diagnosis and treatment. Using screening with PSA, 99% of prostate cancers can now be diagnosed at a clinically localized or potentially curable stage. Over a 11-year period starting in 1988, the Québec screening study performed among 45 000 men aged 45–80 years has shown that the prostate cancer death incidence has decreased by 64% in men who had screening. The impact of screening, however, requires early application of the most efficacious treatments. In this context, the most important recent therapeutic advance in the field of prostate cancer is androgen blockade, namely medical castration with LHRH agonists, the availability of pure antiandrogens and combined androgen blockade (CAB) using medical or surgical castration in association with a pure antiandrogen. In the six studies performed in localized or locally advanced disease, the improved cancer-specific survival ranges between 37 and 81% at 5 years of follow-up for patients who received androgen blockade. On the other hand, data already available show that long term and continuous (not intermittent) androgen blockade is highly efficient and can achieve long term control or possible cure of localized prostate cancer.

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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. In fact, one out of nine men will be diagnosed with prostate cancer during his lifetime. At the present rate, prostate cancer will kill more than 3 000 000 men among the male population presently living in the United States. The medical and social consequences of this disease are comparable to those of breast cancer in women.

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 of treatment of localized prostate cancer on survival (Kolata, 1987;

Middleton et al., 1995). Such an absence of studies has been erroneously interpreted as being equivalent to the availability of negative data while, in fact, negative data have never been obtained for any form of treatment of localized prostate cancer.

Most fortunately, six prospective randomized trials have recently demonstrated that an important prolongation of life was obtained in localized prostate cancer treated with androgen blockade (Bolla et al., 1997; Pilepich et al., 1997; Granfors et al., 1998; Labrie et al., 1999a; Messing et al., 1999; Hanks et al., 2000). Quite remarkably, in various studies, the improved cancer-specific survival ranges between 37 and 81% at 5 years of follow-up in patients with localized disease who received androgen blockade compared with controls not immediately treated with androgen blockade. In fact, the first prospective and randomized studies that have shown statistically significant benefits on survival in localized or locally advanced disease are those using androgen blockade.

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Table 1  
Number of TRUS-guided biopsies and positive biopsies to serum PSA and DRE in men who had both exams at all visits at first and follow-up visits

PSA	DRE	First visit						Follow-up visits										
		TRUS			Biopsies			CaP			Biopsies			CaP				
		Visits #	% Visits	#	% TRUS	#	% Biopsies	Visits #	% TRUS	#	% TRUS	#	% Biopsies	Visits #	% TRUS	#	% Biopsies	
-	-	7281						7674										
	+	404	94.3	246	64.6	27	11.0	189	60.8	0.6	0.6	15	33.3	1	6.7			
+	-	1379	94.1	494	38.1	158	32.0	1662	35.1	63.2	63.2	224	38.4	53	23.7			
	+	232	94.8	173	76.6	97	56.1	68	8.2	8.2	8.2	32	74.4	15	46.9			
	Total	9296	20.4	913	48.1	282	30.9	9593				330	41.9	74	22.4			

## 2. Importance of screening for diagnosis at a localized stage

### 2.1. High efficacy of prescreening with PSA

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.

Table 1 describes the relative sensitivity of serum PSA and digital rectal examination (DRE) to detect prostate cancer at first and annual follow-up visits. It can be seen that 255 of the 282 cancers (90.4%) detected at first visits were PSA<sup>+</sup> while only 124 (44.0%) were DRE<sup>+</sup>. At the follow-up visits in men who had DRE and PSA at all visits, 68 were PSA positive and only 6 (8.1%) were missed by PSA and found by DRE, thus demonstrating the unique efficacy of serum PSA to detect prostate cancer, especially at annual follow-up screening visits (Table 1).

The present data show that 344 DREs are required to find one case of prostate cancer at first visit while 1919 DREs are required at follow-up visits. On the other hand, 36 and 141 PSA measurements are required at first and follow-up visits, respectively, to diagnose one case of prostate cancer. Based upon 18 889 visits where men had both PSA and DRE, the present data show that PSA is about ten times more efficient than DRE to detect prostate cancer at a clinically localized and potentially curable stage. Such data support our previous findings (Labrie et al., 1993) as well as those of Shröder et al. and Makinen et al. (Shröder et al., 1998; Makinen et al., 2001; Shröder et al., 2001) which demonstrate the high efficacy of PSA used alone for prostate cancer screening. A most important finding is that only two out of 215 (1.0%) cancers diagnosed at 46 751 follow-up visits were metastatic compared with 6.7% at first visit (Candas et al., 2000).

An important observation based on overwhelming scientific evidence is that PSA can be efficiently used as a pre-screening test for prostate cancer, thus keeping the more costly and less well-tolerated DRE and transrectal ultrasonography (TRUS) as second step procedures (Labrie et al., 1996b; Shröder et al., 1998; Candas et al., 2000; Makinen et al., 2001; Shröder et al., 2001). Using this approach, practically 100% of prostate cancers can be diagnosed at a clinically localized or potentially curable stage, therefore, practically eliminating the diagnosis of metastatic disease (Labrie et al., 1996b; Candas et al., 2000).

As clearly suggested in our previous reports (Labrie et al., 1996b; Candas et al., 2000) and well demonstrated by the present update and extension of the previous data, the most cost-effective strategy for early diagnosis of prostate cancer is measurement of serum PSA as first

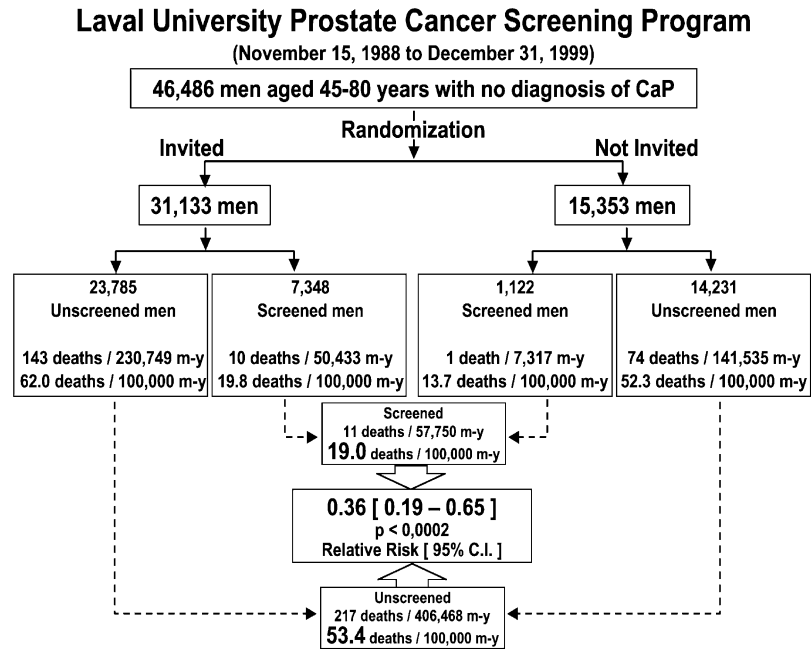


Fig. 1. Summary of data of the Laval University Prostate Cancer Screening Program (November 15, 1988–December 31, 1999).

line or as a prescreening. The same conclusion has been reached in two other large scale screening studies (Shröder et al., 1998; Makinen et al., 2001; Shröder et al., 2001). A similar conclusion has been reached by Hugosson et al. (2000) who wrote: “PSA seems to be excellent as a prescreening test to identify the population at risk and which needs further evaluation (Bangma et al., 1995; Lodding et al., 1998)”. Following this strategy, we have estimated that the costs for finding one case of prostate cancer at first and follow-up visits are estimated at \$2420 and \$7105, respectively (Candas et al., 2000).

### 3. Major impact of screening on survival

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. Fig. 1 shows the breakdown of the numbers according to original randomization and actual participation to screening. In the group invited for screening, 7348 (23.6%) men were screened at our prostate clinic from November 15, 1988 through December 31, 1999. On the other hand, 1122 men (or 7.3% of the initial control group of 15 353 men not invited for screening) presented

at the clinic for screening, despite being not invited by letter.

Ten 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 19.0 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) (Fig. 1). 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.

Among the 15 353 men not invited for screening, 1122 came on their own to the clinic for screening (Fig. 1). Among these men, one died from prostate cancer, thus resulting in an exposure of 7317 man-years in this group of not invited men who were screened. On the other hand, in the group of men invited for screening, 23 785 did not respond to the invitation. Thus, when analyzing the data with respect to the intervention rather than the original group of randomization (Fig. 1), there were 11 deaths in the 8470 men who were actually screened with an exposure of 57 750 man-years. On the other hand, 217 men died from prostate cancer during the 406 468

man-years of exposure in the group of men who were not screened. These data result in a 64% reduction in prostate cancer mortality ( $P = 0.0002$ ) or a relative risk of 0.36 (95% confidence interval = 0.19–0.65) (Fig. 1).

#### 4. Androgen blockade and its efficacy

##### 4.1. Medical castration with LHRH agonists

The discovery by our research group at the Laval University Medical Research Center in Quebec City that medical castration can be easily and very efficiently achieved in men using the well tolerated luteinizing hormone-releasing hormone (LHRH) agonists (Labrie et al., 1980; Faure et al., 1982; Labrie et al., 1982; Tolis et al., 1982) has eliminated the previous limitations associated with blockade of testicular androgens, namely the psychological problems of surgical castration and the serious and even life-threatening side effects of high doses of estrogens on the cardiovascular system (VACURG, 1967; Robinson and Thomas, 1971; Peeling, 1989). The availability of the well tolerated medical castration with LHRH agonists (Labrie et al., 1980) has thus 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.

#### 5. Local biosynthesis of androgens: intracrinology

Following the discovery of the castration effect of LHRH agonists (Labrie et al., 1980), the next most important advance made in our understanding of the biology and endocrinology of prostate cancer and its impact on cancer treatment is probably 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 (Labrie et al., 1985), the main secretory product of the testicles. Such high circulating levels of DHEA-S (and also DHEA) provide high amounts of the prohormones 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 (Labrie et al., 1988; Labrie, 1991). The active androgens made locally in the prostate exert their action by interacting

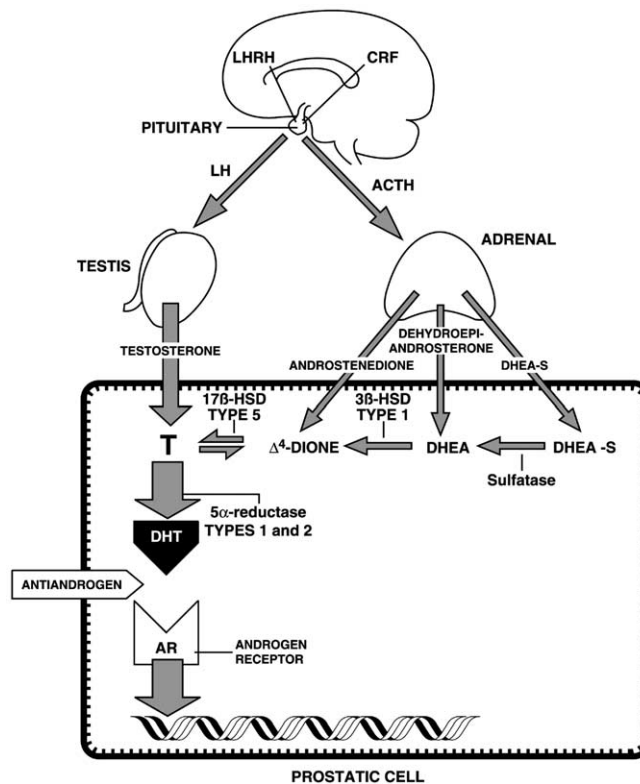


Fig. 2. Intracrine activity of the human prostate or biosynthetic steps involved in the formation of the active androgen dihydrotestosterone (DHT) from testicular testosterone as well as from the inactive adrenal precursors DHEA, DHEA-sulfate (DHEA-S), and 4-dione in human prostatic tissue. 17β-HSD = 17β-hydroxysteroid dehydrogenase; 3β-HSD = 3β-hydroxysteroid dehydrogenase/Δ<sup>5</sup>-Δ<sup>4</sup>-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 and DHEA-sulfate (DHEA-S), 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.

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 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 at a level comparable to the androgens of testicular origin.

### 5.1. Combined androgen blockade versus monotherapy in advanced prostate cancer

The first treatment shown to prolong life in prostate cancer is the combination of an LHRH agonist (blocker of androgen secretion by the testes; Labrie et al., 1980) with a pure antiandrogen such as flutamide, nilutamide (or bicalutamide). When associated with castration which eliminates the androgens of testicular origin, these compounds block the action of the androgens produced locally in the prostate (Labrie et al., 1982, 1985; Crawford et al., 1989; Denis, 1993; Bennett et al., 1999).

An interesting observation is that the demonstration of the benefits of combined androgen blockade (CAB) have been obtained 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 have both been 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 (Crawford et al., 1989; Denis et al., 1993; Janknegt et al., 1993; Caubet et al., 1997; Dijkman et al., 1997; Denis et al., 1998; Bennett et al., 1999; Prostate Cancer Trialists' Collaborative Group, 2000). In the first large scale randomized study, patients who were treated with flutamide and the LHRH agonist Lupron lived, on average, 7.3 months longer than those who received Lupron plus placebo (Crawford et al., 1989).

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 (Crawford et al., 1989; Denis et al., 1993; Janknegt et al., 1993; Caubet et al., 1997; Dijkman et al., 1997; Denis et al., 1998; Bennett et al., 1999; Prostate Cancer Trialists' Collaborative Group, 2000). 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, bicalutamide or nilutamide) to castration. These data demonstrate the particularly high level of sensitivity of prostate cancer to androgen deprivation, considering that such statistically significant benefits are obtained, even at the very advanced stage of metastatic disease.

Bennett et 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. As shown in Table 2, similar benefits have been obtained in favor of flutamide plus castration versus castration alone in the meta-analysis of Bennett et al. (1999) and that of the Prostate Cancer Trialists' Collaborative Group (PTCTG; Fig. 3). As mentioned above and predicted (Labrie and Crawford, 1995), the difference has also become statistically significant in the most recent PCTCG analysis (2000).

The US FDA recently approved a new labelling for Herceptin that states that women with HER2 (human epidermal growth factor 2)—positive metastatic breast cancer treated with Herceptin plus chemotherapy have a 24% increase in median survival over those receiving chemotherapy alone (median 25.1 vs. 20.3 months). (SCRIP, 2001). “The survival benefit demonstrated by Herceptin represents one of the largest improvements made in the treatment of metastatic breast cancer in over four decades,” the company claims (SCRIP, 2001). In fact, it is most surprising to realize how different are the attitudes in two closely related cancers, namely breast and prostate cancer. Thus, while 4.8 months of additional survival are considered a major achievement for women with advanced breast cancer, the same survival advantage achieved in men at the same stage of prostate cancer is not considered by many as being of valuable clinical significance. The surprise is even greater when one compares the cost of Herceptin versus that of an antiandrogen.

With the clinical data summarized above, the controversy concerning CAB should be part of history and the addition of a pure antiandrogen should be recognized by all as providing an advantage of 3–6 months of life in metastatic disease at a time when no alternative treatment even exists. When considering cancer-specific survival, the data show that 6–12 months of life are added by simply adding a pure antiandrogen to medical or surgical castration (Dijkman et al., 1997; Bennett et al., 1999; Prostate Cancer Trialists' Collaborative Group, 2000; Brawer et al., 2001).

### 5.2. Major benefits of androgen blockade in localized disease

Despite the recent advance in the treatment of metastatic prostate cancer using LHRH agonists (Labrie et al., 1980, 1996a) or surgical castration in association with a pure antiandrogen (Labrie et al., 1982; Crawford et al., 1989; Dijkman et al., 1997; Denis et al., 1998; Bennett et al., 1999), it is well recognized that the only

Table 2

Hazard ratios (RR) and 95% of confidence intervals (CIs) using alternative methods for estimating hazard ratios for survival data (Bennett et al., 1999) and comparison with results from the 2000 PCTCG analysis

Year of analysis	Method of metaanalysis	RR	95% CI	Number of studies
Bennett et al. (1999)	Literature-based	0.90	0.79–1.00	9
PCTCG (2000)	Patient-level	0.92 <sup>a</sup>	0.89–0.95	12

*2p* = 0.02

<sup>a</sup> In favor of Flutamide+castration vs. castration alone.

means of achieving an important reduction in prostate cancer mortality is treatment of localized disease (Labrie et al., 1997). 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 (Lee et al., 1989), coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy and endocrine therapy (Labrie et al., 1994, 1997; Laverdiere et al., 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 3). When considering deaths from prostate cancer at 5 years of follow-up, decreases ranging from 37 to 81% were observed in the various studies. In the EORTC (European Organization for Research and Treatment of Cancer) trial performed in stage T<sub>3</sub> 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 (Bolla et al., 1997). Death from prostate cancer at 5 years was thus decreased by 77% by androgen blockade (Table 3). On the other hand, a 37% improvement in cancer-specific survival at 5 years has been found in RTOG trial 08351 in the subgroup of high Gleason score patients who received androgen blockade (LHRH agonist) indefinitely or until progression in association with radiotherapy versus radiotherapy alone (Pilepich et al., 1997). In another study, a 54% decrease in cancer-specific death has been found in patients with an 8–10 Gleason score who had androgen blockade (Hanks et al., 2000), while Granfors et al. (1998) have found a 39% decrease in cancer-specific death when castration was added to radiotherapy versus radiotherapy alone.

### Mortality results from the 12 randomised trials of CAB (Castration + FLUTAMIDE) versus Castration alone in advanced prostate cancer

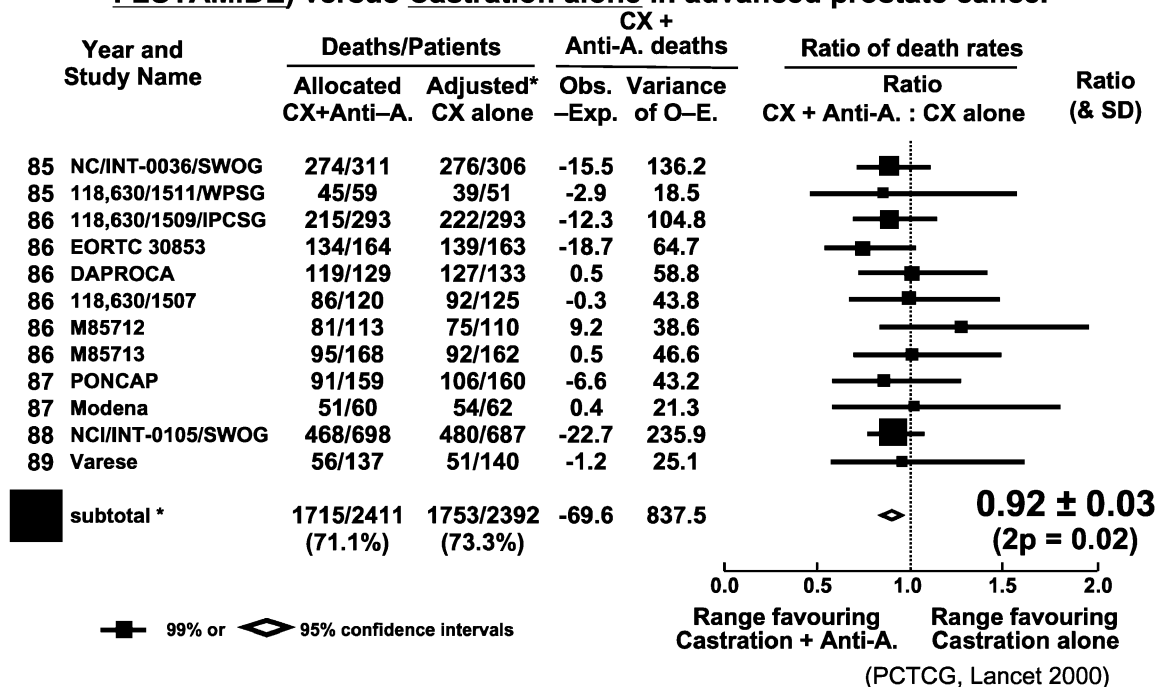


Fig. 3. Mortality results from the 12 randomized trials of CAB (Castration + Flutamide) vs. Castration alone in advanced prostate cancer (Prostate Cancer Trialists' Collaborative Group, 2000).

Table 3  
Randomized studies showing survival benefits following treatment of localized cancer-specific prostate cancer

Study	Benefits
EORTC (Bolla et al., 1997)	77% decrease in cancer-specific death ( $P = 0.01$ )
RTOG trial (Pilepich et al., 1997)	37% decrease for Gleason score 8–10 ( $P = 0.03$ )
Quebec Screening Trial (Labrie et al., 1999a)	64% decrease in cancer-specific death ( $P = 0.0002$ )
Messing et al. (1999)	81% decrease ( $P = 0.001$ )
Granfors et al. (1998)	39% decrease in cancer-specific death ( $P = 0.06$ )
Hanks et al. (2000)	59% decrease for Gleason score 8–10 ( $P = 0.007$ )

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 (Messing et al., 1999). 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 64% 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. 1) can only be due to the treatments used.

It is of interest to mention that in a study of 3603 men with localized or locally advanced prostate cancer, monotherapy with bicalutamide (150 mg daily) reduced objective progression by 43% ( $P < 0.0001$ ) (Wirth et al., 2001). In that study, prior therapy with a curative intent had been given to 64% of patients (44% prostatectomy, 18% radiotherapy and 2% prostatectomy + radiotherapy), while 36% had been followed by watchful waiting. These results were obtained after a median follow-up of 2.6 years. A similar benefit of androgen blockade was obtained for patients who received treatment with a curative intent or those followed by watchful waiting. Although follow-up is too short to analyse the effect on survival, the 43% decrease in the rate of progression of disease in men who received early treatment with the antiandrogen is strongly suggestive of a future positive impact on survival.

It is thus not surprising that hormone therapy alone is more and more recognized as highly efficient in localized or locally advanced prostate cancer (Brawer et al., 2001). 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) develops 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.

## 6. Possibility of cure of prostate cancer with long term combined androgen blockade

A word of caution is extremely important concerning the 10–20% increase in cancer-specific survival achieved in advanced metastatic disease with CAB compared with monotherapy (Table 2, Fig. 3). In fact, the benefit demonstrated with CAB in patients suffering from advanced disease should not be transferred as such to patients with localized disease where much more positive results are expected. Thus, in analogy with the treatment of all other types of cancers, the beneficial effects are much greater when the same treatment is applied at an earlier stage of the disease. In this respect, as summarized later, recent data clearly indicate that CAB might well be the best treatment for localized prostate cancer (as already recognized for advanced disease). Moreover, with long-term treatment of localized prostate cancer, the evidence obtained even suggests that long term control or cure of the disease can be obtained in the majority of patients (Labrie et al., 1999b; Labrie, 2000b).

While the majority of studies performed so far in localized prostate cancer have used monotherapy (medical or surgical castration)(Bolla et al., 1997; Pilepich et al., 1997; Granfors et al., 1998; Labrie et al., 1999a; Messing et al., 1999; Hanks et al., 2000), there are good reasons to believe that even better results will be obtained with more complete or CAB (Labrie et al., 1985; Caubet et al., 1997; Bennett et al., 1999; Labrie, 2000a,b; Prostate Cancer Trialists' Collaborative Group, 2000). Since we had already obtained evidence for the high efficacy of long term and continuous CAB in localized prostate cancer (Labrie et al., 1999b), 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 administered for periods up to 11.3 years.

In 26 patients with clinically localized prostate cancer who received CAB with the antiandrogen flutamide and an LHRH agonist as only treatment for as long as 11.7 years (median = 7.2 years), the first and so-far only progression of the cancer indicated by a rise of serum PSA while the patient was receiving CAB occurred in only one patient believed to have been on CAB for 7 years and 4 months of treatment. Since serum PSA had remained undetectable for more than 4.0 years under continuous CAB treatment in 25 patients, CAB was

stopped in 20 of them. The median follow-up post-cessation of CAB is 4.9 years (range 0.0–8.2 years). Progression or biochemical failure illustrated by a PSA rise has occurred in only four cases following cessation of CAB. Ten patients are still alive with low PSA after a median duration of follow-up of 4.9 years after cessation of CAB and after a median survival of 14.6 years after starting CAB.

Of 26 patients with stage C or T3 prostate cancer at diagnosis who had undetectable serum PSA for a median duration of 9.9 years (range 3.8–11.3 years) while receiving continuous CAB and who all stopped androgen blockade, serum PSA increased above 1.0 ng/ml in only six of them (23%) during a median follow-up of 5.6 years (range 0–9.1 years) after cessation of CAB. Serum PSA thus remained undetectable in 20 patients (77%) up to a median follow-up of 5.6 years.

Much less positive results in terms of biochemical failure were observed, however, in patients who had received CAB for only 1 year before stopping treatment. In fact, in this group of 11 patients treated with CAB for a short period of only 1.0 year, serum PSA increased in all cases within 1 year after cessation of CAB, thus indicating that cancer had remained viable in all cases, despite PSA being undetectable.

It is of major interest to see how PSA failure is inversely correlated with the duration of continuous CAB administration before cessation of treatment. In fact, of the 57 patients with B2/T2 or C/T3 disease treated continuously with CAB for various time intervals up to 11.7 years, only two PSA rises have occurred in the 33 patients who had received CAB for more than 6.5 years before stopping treatment. When taking 5 years with no PSA rise after cessation of CAB as parameter of long term control or possible cure of the cancer, the no failure rate is 90% (18/20) in this group of patients (Fig. 4). When looking in more detail at this group of patients, the no failure rate is 87.5% (7/8) for patients previously treated with CAB for 6.5–10 years before stopping treatment, while it is 91% (11/12) for those previously treated for 10–11.7 years.

Based upon the above-described data, it can be estimated that a period of more than 6 years of continuous CAB is required to efficiently control localized prostate cancer. At approximately 6 years of treatment, long-term control or possible cure of the cancer appears to be achieved in approximately 50% of cases. However, as shown in Fig. 3, when CAB is continued further, a much higher rate of success is achieved with an approximately 90% cure rate at treatment durations ranging from 6.5 to 11.7 years. In clinical practice, one possibility is to stop treatment at 6 years, thus achieving the required long term control of cancer in approximately 50% of cases. In the event of a PSA rise expected in the other 50% of patients, the same CAB should be re-administered without delay for

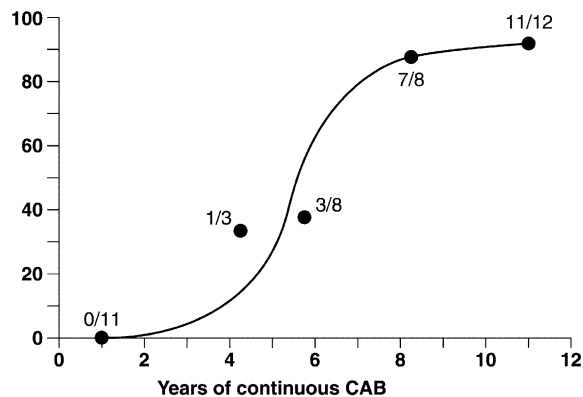


Fig. 4. Effect of duration of treatment of localized prostate cancer with continuous CAB on the probability of long term control or 'cure of the disease' illustrated by no recurrence of PSA rise for at least 5 years after cessation of CAB. The point at 4.75 years of treatment (33%) refers to the three 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 12 patients treated for 10–11.7 years with continuous CAB before stopping treatment. All patients were followed for at least 5 years after continuous CAB or until PSA rise. Only one patient has died from prostate cancer while 18 have died from other causes.

another 3 years. A major mistake made so far, starting with our own neoadjuvant trial started in 1988 (Labrie et al., 1994), is that CAB has generally been administered for much too short periods of time.

With the knowledge of the above-described data, it seems reasonable to suggest that the minimal duration of continuous CAB 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 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 and before metastases reach the bones when cure has become an exception.

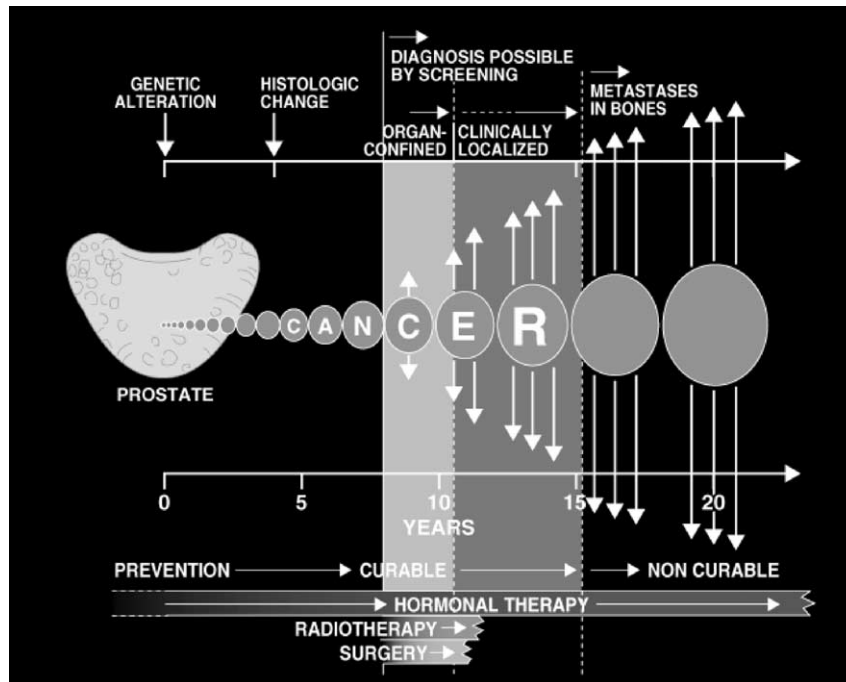


Fig. 5. Schematic representation of the evolution of prostate cancer from the time of appearance of the first genetic change which is followed by a series of cell divisions and other mutations, thus eventually resulting in a cancer cell. During the following years, the cancer cells can only be seen by gene markers and then, histological changes become visible. However, it is only after many years of evolution that the tumor reaches a relatively large volume ( $0.3 \text{ cm}^3$ ) which becomes detectable by screening with PSA, DRE and/or transrectal echography of the prostate. Depending upon the genes involved, the rate of cancer growth is variable between individuals and the scale shown is an estimated average. It is important to mention that when diagnosis has become possible by screening, approximately 60% of the cancers have already migrated outside the prostate and are no longer organ-confined. The diagram also indicates the time when each treatment can be most efficiently used. Radical prostatectomy can cure the disease when the cancer is organ-confined and no cancer cell has migrated outside the prostate. Radiotherapy and brachytherapy (seed implants) are believed to have an efficacy comparable to that of surgery. Hormonal therapy, more specifically CAB offers a high possibility of cure of the disease when treatment is started before the cancer migrates to the bones, even if it has migrated in the area surrounding the prostate. Hormonal therapy, however, must be continuous and long-term but not intermittent. At the advanced stage of bone metastases, only CAB has been shown to prolong life compared with monotherapy but the possibility of a cure is minimal. Data obtained in localized disease show that long term CAB can cure the disease in the majority of cases. Much remains to be understood about the treatment of localized disease but this diagram is drawn according to the best knowledge available.

## 7. Conclusion

While showing the high efficacy of hormonal therapy in localized prostate cancer, the present data clearly indicate that long-term treatment, similar to the 5 years of Tamoxifen in breast cancer, is required for optimal control of prostate cancer. Great caution should be taken, however, when using serum PSA as surrogate marker. In fact, serum PSA rapidly decreases to undetectable levels under androgen blockade although the cancer remains present for much longer periods of time, usually many years. For this reason, intermittent therapy should not be recommended outside prospective and randomized clinical trials.

Fig. 5 is a schematic representation of the evolution of prostate cancer through its various stages of progression. This figure also indicates the timing of efficient screening and of the various treatment alternatives. It is

clear that the usefulness of screening and early diagnosis of prostate cancer is entirely dependent upon the timing of diagnosis and the choice of the treatment used. Since the majority of cancers can now be diagnosed at the clinically localized stage with the available screening tests (Labrie et al., 1996b), the priority should focus on the choice of the best treatment for each patient. In addition to the high mortality rate, prostate cancer is associated with much suffering and a poor quality of life and high costs in those developing progressive disease (Carlsson et al., 1989; Aus et al., 1995; Otnes et al., 1995)

With early diagnosis and treatment, as clearly demonstrated in the first randomized screening study (Labrie et al., 1999a) (Fig. 1), death from prostate cancer should decrease dramatically and should even become rare. Since prostate cancer is expected to be the cause of death of 3 million men presently living in the United States, a

64% decrease in prostate cancer death (Fig. 1) corresponds to a saving of approximately 2 million lives in the United States alone. Further progress in the diagnosis and treatment of localized prostate cancer should improve these figures even further.

With the present knowledge, it is 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. It is also clear from the data summarized above that CAB could well be the most efficient therapy of localized prostate cancer while it has already been recognized as the best therapy for metastatic disease.

Clearly, the rational use of the presently available diagnostic and therapeutic approaches could decrease prostate cancer death by at least 50% (Labrie et al., 1996b, 1999a). As an example, between 1991 and 1999, the death rate from prostate cancer has decreased by 38% in Québec City and its metropolitan area (Candas and Labrie, 2000) while the death rate has decreased by 64% in the group of men who have been screened.

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