

Screening and Early Hormonal Treatment of Prostate Cancer Are Accumulating Strong Evidence and Support

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BACKGROUND. I review the data published during the last 5 years on the effects of early treatment of prostate cancer on survival.

METHODS. Data from prospective and randomized studies as well as from population-based studies are presented.

RESULTS. Two studies (European Organization for Research and Treatment of Cancer and Radiation Therapy Oncology Group) in stage T3 disease have shown that long-term (3 years or indefinite, respectively) androgen blockade prolongs life in patients receiving androgen blockade in addition to radiotherapy compared to radiotherapy alone. In the UK Medical Research Council study, androgen blockade at diagnosis of locally advanced or asymptomatic patients decreased cancer-specific death by 21% compared to delayed treatment. A 69% decrease in prostate cancer death was observed in the Quebec Randomized Prostate Cancer Screening Study. Population-based studies in Sweden and Denmark have shown that 62% and 63%, respectively, of patients diagnosed with localized prostate cancer will die from the disease if not treated immediately. Decreases in prostate cancer death rate of 6.3–23% have been found between 1991–1997 in the US and Canada, respectively.

CONCLUSIONS. Treatment of localized disease has been shown in all the available randomized studies to cause a marked decrease in prostate cancer death. Simple use of the available screening procedures and treatments for localized prostate cancer could cause a dramatic decrease in prostate cancer death. *Prostate 43:215–222, 2000.*

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KEY WORDS: screening; prostate cancer; early diagnosis; early treatment; survival; androgen blockade

INTRODUCTION

Despite the well-recognized fact that the only possibility of a cure in prostate cancer is early treatment, there is probably no medical field more controversial than screening for prostate cancer. It should be added that since prostate cancer almost always develops insidiously without signs or symptoms until the noncurable stage of metastases in the bones, early treatment or cure of prostate cancer will never be possible without screening in asymptomatic men.

Prostate cancer is the cancer most frequently diagnosed and the second cause of cancer death in men in North America [1]. It was predicted that 37,800 men would die from prostate cancer in the United States in

1999, while 43,700 deaths were estimated for breast cancer during the same time period [1]. In fact, 1 in 9 men will be diagnosed with prostate cancer during his lifetime. At the present rate, of the male population living in the United States, prostate cancer will kill more than 3,000,000 men. Prostate cancer is thus a major medicosocial problem in urgent need of significant improvement in diagnosis and treatment.

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TABLE I. Randomized Studies Showing Survival Benefits Following Treatment of Localized or Asymptomatic Metastatic Prostate Cancer

Authors	Benefits
EORTC trial (Bolla et al., 1997) [9]	45% improved overall survival ($P = 0.001$) 77% decrease in cancer-specific death
RTOG trial (Pilepich et al., 1997) [10]	20% improved overall survival for Gleason score 8–10 ($P = 0.03$)
Medical Research Council study (MRC Trial, 1997) [11]	21% decrease in cancer-specific deaths ($P = 0.001$)
Quebec screening study (Labrie et al., 1999) [12]	69% decrease in cancer-specific death ($P < 0.01$)

Since even the best treatment of advanced or metastatic prostate cancer can only prolong life with minimal or no possibility of a cure [2–7], it is somewhat difficult to understand why early diagnosis and treatment, an approach recognized for most if not all other types of cancers, is not considered as the first objective in the field of prostate cancer.

Since the negative opinions on screening have been mainly expressed in review articles while the positive results about the benefits of early treatment have been described individually in more specialized and less widely accessible publications, it seems appropriate to summarize in a short review the positive evidence accumulated by many groups during the last 5 years.

RESULTS AND DISCUSSION

Early Treatment Prolongs Life

The major source of controversy concerning early diagnosis and early 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 [8]. Such an absence of studies and the consequent absence of results have been erroneously interpreted as being equivalent to the availability of negative data, despite the fact that negative data have never been obtained.

Fortunately, two prospective randomized trials have recently demonstrated for the first time that not only quality of life but, most importantly, prolongation of life was observed in localized prostate cancer patients treated with androgen blockade. In the European Organization for Research and Treatment of Cancer (EORTC) trial performed in stage T_3 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 [9] (Table I). Death from prostate cancer at 5 years was decreased by 77% by androgen blockade. A 20% improvement in overall

survival at 5 years has also been found in the Radiation Therapy Oncology Group (RTOG) trial 08351 in the subgroup of high Gleason score patients who received androgen blockade (LHRH agonist) indefinitely or until progression [10].

Following a long controversy, a large prospective and randomized clinical trial performed by the Medical Research Council Prostate Cancer Working Party Investigators Group [11] has shown the benefits of early androgen blockade in a study of 938 patients with locally advanced or asymptomatic metastatic disease. The patients were randomized to immediate androgen blockade (orchiectomy or LHRH agonist) vs. treatment deferred until symptoms developed. Marked benefits of early treatment were observed on time to progression and development of pain. Complications from metastatic disease were twice as frequent in the deferred group and, most importantly, a 21% decrease in cancer-specific death was observed in patients who had early androgen blockade.

It can be added that the 69% decrease in the incidence of death from prostate cancer observed during the first 8 years of our randomized and prospective study on prostate cancer screening [12] can only be due to the treatments used.

Screening Does Not Detect Small and Insignificant Cancers

An argument frequently cited against screening is that screening could detect insignificant cancers. In fact, it is known that one third of men older than 50 years have incidental prostate cancer found at autopsy while, on the other hand, only 10% of men develop clinical prostate cancer during their lifetime [13]. This apparent paradox has been used as an argument against screening by suggesting that screening would automatically detect the small and still insignificant cancers which are found at autopsy or by transurethral resection of the prostate for treatment of benign prostatic hyperplasia, thus potentially leading to unnecessary treatment. The facts, however, are quite different: the available screening techniques, namely,

prostatic-specific antigen (PSA), digital rectal examination (DRE), and transrectal ultrasonography of the prostate (TRUS), do not detect such small autopsy cancers [14–16]. In fact, screening does not detect cancers having a diameter smaller than 0.75 cm when random or sextant biopsies are only performed in patients having serum PSA > predicted PSA and/or positive DRE in the absence of hypoechoic area at TRUS [16]. More than 92% [17] and more than 90% [18] of PSA-detected cancers have features typical of potentially aggressive cancers. It is now recognized that only approximately 7% of cancers detected by screening are microfocal and low-grade [17,19,20].

A relevant and dependent question is, what will be the influence of screening on the incidence of prostate cancer? While a prevalence of 3.0% of prostate cancer has been found at first screening of asymptomatic men aged between 45–80 years, the incidence of prostate cancer at annual follow-up visits markedly decreased to only 0.52% [12]. Assuming the same average annual incidence of prostate cancer during 20 years of annual screening, localized prostate cancer would be found in 10.4% of men, a value not truly different from the expected 10% incidence of prostate cancers already observed in the absence of screening. It is thus extremely important to realize that screening, performed as described [12,21], does not detect small and insignificant cancers and does not significantly increase the number of men diagnosed as having prostate cancer during their lifetime. In fact, it is important to mention that the available diagnostic techniques cannot detect stage A₁ prostate cancer. These early cancers are detected incidentally by transurethral resection of the prostate that primarily samples the transition zone where 20% of the cancers originate [22,23].

The lower limit of 0.3 cc in the volume of cancers identifiable by the available detection or screening techniques results in the diagnosis of relatively large cancers [24], thus eliminating the argument that detection or screening discovers cancers of no significance to the health or even the life of a patient having an at least 5–10-year life expectancy. A strong argument supporting these findings is provided by the observation that 75% of men who developed prostate cancer with an elevated PSA died from this cancer [25].

Early Treatment Shows Important Benefits for Survival in a Series of Population-Based Studies

It is now well-demonstrated in analyses performed in Sweden and Denmark, two countries having reliable and high-quality cancer and death registries, that patients who are diagnosed with localized prostate cancer with a life expectancy of more than 10 years

TABLE II. Percentage of Patients (Who Lived 10 Years or More After Diagnosis) Dying From Prostate Cancer in Population-Based Studies

Denmark (Brasso et al., 1999) [29]	61.8%
Sweden (Aus et al., 1995) [26]	62.0%
Sweden (Hugosson et al., 1995) [27]	63.0%

have a high risk of dying from prostate cancer if it is not treated immediately [26–29]. It is even concluded from the studies in Sweden that patients diagnosed with localized prostate cancer and not treated immediately will die from prostate cancer if they live long enough [26,27].

Since patients diagnosed with prostate cancer and surviving for at least 10 years are likely to have localized disease when diagnosed, the outcome of 2,570 such patients registered between 1943–1986 in the Danish Cancer Registry was studied [29]. This population of men who survived more than 10 years corresponds essentially to the group of men who are considered candidates for radical therapy.

An overall excess mortality compared to the general population of 1.58 (1.51–1.65, 95% confidence intervals) was found. In fact, of the patients who died 10 years or more after diagnosis, 42.7% had prostate cancer as direct cause of death and 19.1% as contributing cause of death, for a total of 61.8% of deaths having prostate cancer as direct or contributing cause of death (Table II). Of the patients aged between 55–74 years, 64.4% died from prostate cancer, while 51.5% of the patients 75 years old or older died from prostate cancer [29]. It should be mentioned that no curative-intent surgery was performed in Denmark before 1995, and radiation therapy was used rarely (less than 1% of cases).

The 61.8% of patients dying with prostate cancer as direct or contributing cause of death in the Denmark study is not different from the 62% and 63% reported in Sweden for a comparable group of patients [26,27]. Of major importance is the observation that a patient must be older than 75 years at diagnosis to have a risk of dying from prostate cancer lower than 50% [26,30]. In other words, at all ages below 75 years, patients diagnosed as having nonmetastatic prostate cancer and who do not receive immediate therapy have a greater than 50% risk of dying from prostate cancer. Even when diagnosis was made after age 75 years, nearly one third of patients died from prostate cancer.

Two other recent population-based studies have shown an improved cause-specific survival after 10 years in patients with clinically localized prostate cancer treated with curative intent compared to those treated conservatively [31,32]. In fact, using the 146,979 prostate cancer patients from the 1973–1990

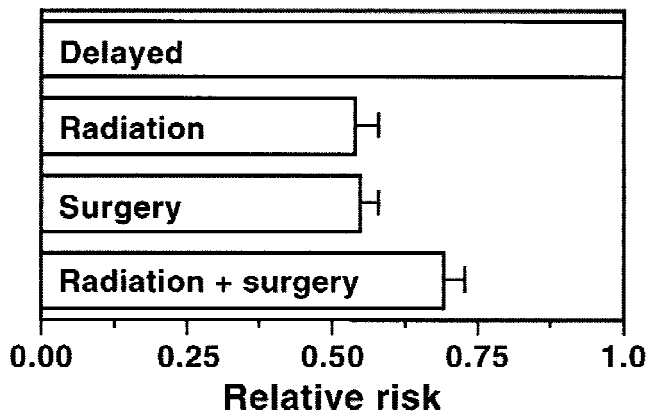


Fig. 1. Cancer-specific mortality in 104,577 patients with in situ, localized, or regional prostate cancer according to treatment [32].

public use tape of the Surveillance, Epidemiology and End Results (SEER) program, a survival analysis and multivariate proportional hazards modeling were performed to estimate the relative risk of disease-specific mortality [31]. It was then found that of the 104,577 patients with in situ, localized, or regional prostate cancer, median survival was 50 (49–52, 95% confidence interval) months in those who had no immediate treatment, 73 (72–74) months in those who had surgery, 103 (101–107) months in those who had radiation therapy, and 93 (91–93) months in those who had both surgery and radiation therapy.

The relative risk of overall survival was calculated at 0.41 (0.40–0.43), 0.66 (0.64–0.68), and 0.49 (0.47–0.50) for radiation, surgery, and radiation + surgery, respectively, compared to 1.0 in the group of men not treated immediately [31]. When cancer-specific survival was considered, treatment had a major impact on survival, the relative risk being 0.54 (0.51–0.58), 0.55 (0.53–0.58), and 0.69 (0.65–0.73) for radiotherapy, surgery, and radiotherapy + surgery, respectively, 1.0 being the value for the group of men who had no immediate treatment (Fig. 1).

While prostate cancer death rate increased between 1980–1992 in Olmsted County (Minnesota), a 22% decline was seen between 1993–1997 [33] (Table III). More generally, data from the National Center for Health Statistics indicate that the prostate cancer death rates for the United States declined 6.3% between 1991–1995 [34,35]. In Quebec, the prostate cancer death rate has decreased by 23% between 1991–1997, while in Canada overall, a decrease of 9.6% was found between 1991–1996 [36].

The Very High Risk of Watchful Waiting: Prostate Cancer Grows Slowly But Steadily and Irremediably, If Left Untreated

While deferred treatment or watchful waiting can sometimes be an approach which can be considered in

TABLE III. Decrease in Prostate Cancer Death

Site	Period	Percentage
USA (Hoeksema and Law, 1996) [34], (Wingo et al., 1998) [35]	1991–1995	6.3
Canada (Meyer et al., 1999) [36]	1991–1996	9.6
Quebec (Meyer et al., 1999) [36]	1991–1997	23.0
Olmsted County (Roberts et al., 1999) [33]	1993–1997	22.0

men having a short life expectancy and diagnosed with low-grade localized disease, the data summarized above clearly limit the indication of this approach to a small proportion of patients who should, in any case, be well-informed about the recently available data and the risks involved in deferring treatment.

In fact, the controversy over screening largely results from the publication of a few much-publicized reports on the potential value of deferred treatment for localized prostate cancer in selected men older than 70 years. The questionable conclusions derived from case reports have been erroneously extended to prostate cancer in general. In fact, all these reports are from uncontrolled studies which simply describe data obtained from small series of highly selected patients. These case report studies were erroneously taken as representative of the standard evolution of untreated patients while, on the contrary, all these patients were selected for deferred treatment because of a more favorable prognosis. Moreover, almost all such patients were treated at first sign of progression [37–45].

Somewhat surprisingly, the possibility of deferred treatment in such a highly selected group of men older than 70 years has been used as an argument against screening while, in fact, those data could at best suggest that some selected patients having a life expectancy of less than 10 years could choose deferred treatment despite an important risk of dying from prostate cancer and a very high risk of suffering from metastatic disease within 10 years [38,45]. Those who used these data to argue against screening also missed the fundamental fact that in order to have the possibility of choosing deferred treatment for small and low-grade cancer, screening must be performed in order to detect prostate cancer at such an early stage. In the absence of screening, most men will continue to be diagnosed at an advanced stage of the disease and will continue to die from prostate cancer at the same rate, with no possibility of choosing a treatment for localized disease.

An inescapable conclusion derived from all studies, including those based on watchful waiting [37–45], is that prostate cancer progresses slowly but it irremedi-

ably leads to distant metastases and death if left untreated and sufficient time is available [46]. Such a progressive increase in prostate cancer volume is associated with increased dedifferentiation and malignancy, with a larger number of genetic alterations [47]. When prostate cancer reaches a critical size, it migrates outside the prostate and becomes more dedifferentiated, and a cure is difficult or no longer possible when the cancer has reached the bones [46,48].

As an example of tumors progressing with time, George [49] reported a 84% local progression rate within approximately 4 years, while Adolfsson et al. [40] reported a 55% progression to T₃ within 10 years. The bias towards tumors of low grade in the study of Adolfsson et al. [40] can explain the apparent difference, although the progression rate in Adolfsson et al. [40] is still very high and unacceptable for most patients.

Epstein et al. [50] and Blute et al. [51] have shown that young patients not treated, even with low-grade tumors and in the best prognostic category, will eventually show progression if they survive and are followed for long enough. Similarly, McNeal [52] indicates, "There are not two types of prostate cancers with different biological potential but a single species having a slow growth rate and a logarithmic growth curve. There is a gradual increase in biologic malignant potential which is closely linked to tumor size." In agreement with this conclusion, in men younger than 50 years discovered as having stage A₂ or B prostate cancer, the probability of being alive is 70% at 10 years and 60% at 15 years, thus indicating that the patients remain at risk for death from prostate cancer more than 15 years after diagnosis [53].

Difficulty of Precise Staging of Prostate Cancer

Unfortunately, there are no means of determining with certainty the exact stage or grade of cancer at diagnosis and thus of predicting at a high level of confidence which cancers will become incurable if left untreated for some more time. In fact, the error associated with staging and grading of prostate cancer at diagnosis is large because of the multifocality and heterogeneity of prostate cancer. There is thus an important risk in assuming that an individual having low-grade cancer at needle biopsy has in fact good prognosis cancer(s) at other sites not examined. In fact, the very useful collection of data on deferred treatment made by Chodak et al. [45] shows that 13% of men with grade 1 or 2 prostate cancer will die within 10 years from prostate cancer, while distant metastases will develop in 19% of them. In grade 3 tumors, on the other hand, 63% died from their disease within 10 years, and distant metastases developed in 74% of

cases. Similarly, at 10 years of follow-up of stage B patients treated at signs of progression, 20% died from prostate cancer, while 50% had distant metastases and 70% had local progression [38]. For men younger than 70 years, 10 years of life is a short time.

Even stage A₁ prostate cancer, until recently considered as latent or indolent cancer, has been shown to have metastatic potential. In fact, stage A₁ prostate cancer, which includes moderately or well-differentiated tumors involving less than 5% of the tissue removed for treatment of benign prostatic hyperplasia by transurethral resection or open prostatectomy, was previously regarded as latent and of little clinical significance [54]. Recent studies, however, show that 20% of patients with stage A₁ disease suffered from metastatic progression during a 10-year follow up period [50,51,55].

As mentioned above, it is important to indicate that prostate cancer, even at grades 1 and 2, is a progressive disease and given sufficient time, it will reach the stage of metastasis in the bones and become incurable. The life expectancy and general health status of the patient are thus extremely important in order to decide about immediate therapy or watchful waiting. The large degree of uncertainty of the available prognostic factors further complicates the therapeutic decision for individual patients and greatly increases the risk associated with watchful waiting.

Prospective and Randomized Prostate Cancer Screening Studies

Three prospective and randomized studies for prostate cancer screening are ongoing, namely, the Quebec study, started in 1988, the prostate, lung, colon, and ovarian (PLCO) trial, started in 1995, and the European Randomized Study of Screening for Prostate Cancer (ERSPC), started in 1994. Results from the two last trials are not expected before year 2005.

The 46,193 men aged 45–80 years registered in the electoral roll of Quebec City and its metropolitan area were randomized in November 1988 between screening and no screening in a study aimed at assessing the impact of prostate cancer screening on cause-specific death. At first visit, screening included measurement of serum prostate-specific antigen (PSA), using 3.0 ng/ml as the upper limit of normal and a digital rectal examination (DRE). Transrectal echography of the prostate (TRUS) was performed only if PSA and/or DRE was abnormal and biopsy was then done, if PSA was above the predicted PSA value, or if a hypoechoic image was seen [21]. At follow-up visits, PSA alone was used as prescreening. One hundred thirty-seven deaths due to prostate cancer occurred between 1989–1996, inclusively, in the 38,056 unscreened men, while

only 5 deaths were observed among the 8,137 screened individuals. The prostate cancer death rates during the 8-year period were 48.7 and 15 per 100,000 man-years in the unscreened and screened groups, respectively, for a 69% decrease in deaths from prostate cancer in favor of screening and early treatment ($P < 0.01$).

A recent study offers very important support for the unique role of PSA screening in prostate cancer diagnosis: 75% of prostate cancers that were diagnosed during the 4 years following first PSA measurement had abnormal PSA at the start of the study [25]. Most importantly, men having a serum PSA between 3.01–4.0 ng/ml had an 8.6-fold increased risk of being diagnosed with prostate cancer, while men having a serum PSA between 4.01–10.0 ng/ml had a 22.2-fold increased risk compared to those having serum PSA below 1.0 ng/ml. These risk values are much higher than any other risk factor so far described for prostate cancer or any other type of cancer.

Prostate cancer can be diagnosed by the proposed approach at an estimated cost of \$2,665 per cancer at first visit [16], a value well below the costs estimated at \$10,000 and \$30,000 per case of cervical and breast cancer diagnosed by screening, respectively.

CONCLUSIONS

Despite the significant progress achieved in the treatment of prostate cancer using LHRH agonists [56,57] and antiandrogens [3,4,6,57,58], the only possibility of a significant reduction in prostate cancer death is still treatment of localized disease [59]. Since prostate cancer generally develops insidiously for many years without signs or symptoms until it reaches the noncurable stage of metastases in the bones, screening in asymptomatic men is essential. It is reasonable to suggest that the recently observed decrease in deaths from prostate cancer mentioned above [33–36] is due to earlier diagnosis with serum PSA [21] and transrectal echography of the prostate [60], coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy, and endocrine therapy [59,61–63].

If every man simply follows the recommendations of the American Cancer Society [64] and of the American Urological Association [65], i.e., annual screening starting at age 50 years in the general population and at 40 years for men at high risk, the proportion of localized or potentially curable prostate cancer can be increased from approximately 40% in the absence of screening [66,67] to close to 100% [12,21].

In fact, the use of the diagnostic procedures currently available within community-based populations of healthy men is switching the spectrum of prostatic carcinoma from an advanced stage to a much earlier

stage of the disease at diagnosis. Most importantly, the recent availability of well-controlled and long-term data on the natural history of localized prostate cancer [27,68], as well as the recent first demonstration that treatment of locally advanced prostate cancer can improve survival [9–11], provide irrefutable arguments demonstrating the benefits of treatment of localized prostate cancer at time of diagnosis. As strong support for the crucial role of early diagnosis and treatment, we recently found, in the first prospective and randomized prostate cancer screening study, that early diagnosis combined with treatment of localized disease decreased death from prostate cancer by 69% [12]. With the knowledge of all the above-mentioned data, no valid reason remains to doubt that treatment of clinically localized prostate cancer prolongs survival.

In the United States, it has been estimated that the healthcare costs for the treatment of prostate cancer are \$4.5 billion annually [69]. These costs are largely related to the treatment of advanced disease. In fact, in addition to the major impact in decreasing prostate cancer death [12], the economic savings of early treatment on healthcare costs have been previously discussed [16,26,70–72]. The calculations performed leave little doubt that the strategy based on efficient screening and early treatment, namely androgen blockade, surgery, radiotherapy, or brachytherapy alone or in combination with androgen blockade, should play a key role in the successful fight against prostate cancer, while decreasing costs for the healthcare system and society [7,73,74].

With the above-summarized information, it is reasonable to suggest that 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 an exception. The only way to prevent prostate cancer from migrating to the bones and becoming incurable is diagnosis by screening in asymptomatic men and treatment of localized disease. The use of the available diagnostic procedures and treatments of localized disease could have a major impact on morbidity from prostate cancer, and death from this disease could become a rare event.

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