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Prostate Cancer: To Treat or Not to Treat?

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Article info

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Abstract

Context: To treat or not to treat is one of the most difficult dilemmas facing prostate cancer patients, especially elderly men with early prostate cancer or small cancer that is contained within the prostate.
Objective: The primary objective of this review is to analyse the treatment options for patients with localised prostate cancer. This information can be considered alongside other important factors like natural history of disease and diagnostic tests.
Evidence acquisition: Several randomised and nonrandomised clinical trials published in the literature investigating the natural history of the disease, diagnostic tests, and treatment options for localised prostate cancer have been reviewed for this paper.
Evidence synthesis: Analysis of prostate-specific antigen (PSA) kinetics should play a major role in the management of localised prostate cancer. Trials investigating long-term outcomes of active surveillance are under way.
Conclusion: Taking all these factors into consideration, the data support active surveillance as an appropriate choice for patients with well-differentiated or moderately differentiated, low-volume prostate cancer who have a life expectancy of <10 yr. Men with higher grade tumours and longer life expectancy may be at excess risk of death from prostate cancer if managed with active surveillance.

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1. Introduction

Prostate cancer is a major cause of death among men in European countries, with nearly 145 000 cases and 56 000 deaths in the European Union in 1998. Rates of incidence vary considerably among countries, and these rates appear to be increasing because of more frequent and better diagnostic tests, an aging population, and probably a true increase in incidence [1]. There are no obvious strategies to prevent this disease, so screening or early detection has been considered as a possible intervention to reduce the number of deaths.

The observation of a dramatic increase in the incidence of prostate cancer raises the possibility that many prostate cancer cases detected by PSA testing are overtreated. In other words, many patients may not have become symptomatic despite being untreated. The challenge of managing early prostate cancer is to differentiate patients with

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clinically relevant cancers from those whose ''disease'' is destined merely to be an incidental histologic phenomenon.

1.1. *The natural history of the disease and diagnostic tests*

The natural history of prostate cancer is not fully established. It is well known, however, that prostate cancer often has an indolent natural history. It is grows slowly in many cases and has a long phase in which it remains undiscovered. This long latent phase is potentially advantageous for screening, but it appears that some tumours are very slow growing and may never become clinically important [2,3]. Men with these tumours often die of another cause [4]. The mortality of men with very localised tumours is little different than that of other men [4,5]. On the one hand, the relatively benign course of many tumours means that treatment might not benefit and could harm the men concerned. On the other hand, there is a spectrum of duration and severity in terms of the disease. At present, we can not accurately predict prostate cancer behaviour in an individual, so a standard approach is to offer curative treatment to all men with localised prostate cancer, while acknowledging that this treatment is unnecessary in many cases.

There are, in principle, two tests that may be used in mass screening: prostate-specific antigen (PSA) and digital rectal examination (DRE). The PSA test is simple, cheap, safe, and acceptable; however, the prostatic biopsy required to investigate positive results is less acceptable and carries significant risks. The accuracy (sensitivity and specificity) of the PSA test is difficult to determine [6]. There is no good standard against which to test it, since prostatic biopsy may itself miss 10–30% of cases. Also, biopsies are not normally done on men with a negative change in PSA value, so it is difficult to assess the number of false-negative tests and to measure the sensitivity of the PSA test. Testing does not differentiate between relatively harmless tumours and those that are likely to be fatal; therefore, it is not specific for clinically important disease. DRE is less acceptable and less accurate than PSA testing [6].

PSA testing as a screening tool has the following advantages:

- Earlier stage at diagnosis—more localised disease and less advanced/metastatic disease (stage migration)
- Earlier age at diagnosis
- Lower PSA level at diagnosis
- Improved prostate cancer survival rates.

PSA screening has the following disadvantages:

- Increased detection and treatment of indolent tumours
- Overdiagnosis and overtreatment
- Unclear PSA screening cut-off levels
- Unclear data on prostate cancer survival rates due to lead-time and time-length biases.

The ongoing debate over PSA measurement has only recently begun to incorporate the additional value derived from using PSA kinetics for treatment decision making by patients and doctors.

2. Evidence acquisition

Several randomised and nonrandomised clinical trials published in the literature investigating the natural history of prostate cancer, diagnostic tests, and treatment options for localised prostate cancer were reviewed for this paper.

3. Evidence synthesis

3.1. *Kinetics of prostate-specific antigen*

3.1.1. *Prostate-specific antigen velocity*

PSA velocity (PSAV) is the absolute rate of change in PSA over time. The original description by Carter et al differentiated among men subsequently diagnosed with prostate cancer who had a PSAV $\geq$0.75 ng/ml per year and those who had benign prostatic hyperplasia (BPH) or no appreciable prostatic disease (PSAV $<$0.75 ng/ml per year) [7]. A more recent analysis of the Baltimore Longitudinal Studies of Aging cohort reported that a PSAV $>$0.16 ng/ml per year identified men at considerably higher risk of prostate cancer death [8]. The difficulty with this approach is the confounding effect of the biologic variability of PSA. In the absence of disease, day-to-day variation in PSA has been estimated at 34%. Indeed, an increase of $<$20–46% between two consecutive PSA levels may be due to biologic and analytic variation alone. Infection and prostatic manipulation can also affect PSA levels. It follows that variation is often substantially greater than 0.75 ng/ml per year; this may result in the identification of more patients as having ''rapid rise'' than a normal biologic variation. Therefore, when analysing PSAV data, three or more PSA values should preferably be used, especially in a screening setting.

3.1.2. Prostate-specific antigen velocity: a marker of disease biology?

The role of PSAV prior to treatment with curative intent, for example, radial prostatectomy, in determining subsequent risk of dying of prostate cancer was recently analysed by D'Amico et al [9]. The researchers showed that patients who had large PSA increases in the year before surgery probably had more aggressive forms of cancer, since they died at a higher rate than other patients, even after their prostates where removed. The results suggest that monitoring PSA changes over time (ie, tracking PSAV) will help physicians to assess which patients are at particular risk for prostate cancer and which are most likely to benefit from aggressive therapy. Strikingly, men with a rise in PSA level >2.0 ng/ml had a prostate cancer–specific mortality rate nine times greater than those with a PSAV <2 ng/ml. Nonetheless, with a mean follow-up of 5 yr, <10% of patients with a rapid PSAV actually died of prostate cancer in this series. The take-home message based on this study is that physicians should be encouraged to measure baseline PSA levels of men at age 35, then monitor men through their 40 s to determine risk and appropriate treatment if the cancer appears. As with mammograms, this test should be done yearly to catch the disease when it is curable. In conclusion, the rate at which PSA levels rise may be more important for predicting the danger of prostate cancer than the PSA levels themselves.

3.1.3. Prostate-specific antigen doubling time

PSA doubling time (PSA DT) is the time required for the PSA to double in value. In patients with prostate cancer, PSA increases initially in a linear manner followed by an exponential phase. If it is assumed that PSA is increasing exponentially at the time of diagnosis, then doubling time can be expressed as PSA DT = natural log 2(0.693)/λ, where λ is the slope of log PSA versus time. This method uses all PSA values available. A short doubling time is a surrogate for rapid tumour growth, and a longer doubling time implies a more indolent tumour. An increasing volume of data from the literature (Stamey's trials, the Prostate Cancer Prevention Trial [PCPT], and the Medical Therapy of Prostatic Symptoms [MTOPS] trial) points to prostatic volume rather than prostate cancer as the cause of mild elevation of PSA levels in many men with early cancer [10,11]. Therefore, high baseline PSA levels may delay identification of rapid PSA rise. One proposed solution to this problem is the use of subtracted PSA values, where baseline PSA is subtracted from all subsequent PSA determinations in calculating doubling time. The concept of correcting for baseline PSA level is attractive when comparing follow-up data in patients treated definitively with surgery or with radiation. In the future, it is suggested that the nadir PSA level should be subtracted from the postradiation PSA level before the PSA DT is determined. This ensures that equal PSA DTs are calculated for patients with the same absolute increase in PSA.

3.1.3.1. Prostate-specific antigen doubling time: a predictor of therapeutic outcome. Many attempts have been made to utilise PSA DT to predict treatment outcome prior to definitive therapy. D'Amico et al found that, following radiation therapy for prostate cancer, PSA DT was linearly correlated with the interval to clinical relapse following PSA failure [9]. They suggest that those patients with PSA DT >18 mo could be managed expectantly because their cancers were likely to remain latent. Other researchers (ie, Hanks et al [12]) have also found that pretreatment PSA DT significantly correlated with biochemical recurrence.

3.1.3.2. Prostate-specific antigen doubling time and disease progression. Approximately one-third of patients who undergo radical therapy for prostate cancer will experience biochemical recurrence within 10 yr after surgery. Patients who are thought to have local recurrence, for example, are treated with salvage radiotherapy, whereas those believed to have metastatic disease are treated hormonally; however, the ability to make this crucial distinction accurately is limited. It has been shown that PSAV and PSA DT are useful in monitoring this recurrence and progression following failure of definitive therapy. PSA DT in particular has the ability to identify patients at high risk of rapidly progressive disease. This information should guide treatment decisions about radiation therapy versus androgen suppression therapy for biochemical recurrence, the timing of hormonal therapy, and the use of second-line androgen deprivation.

3.1.3.3. Prostate-specific antigen doubling time and active surveillance. There is an increasing concern that patients with good-risk prostate cancer (Gleason score $\leq$6) are being overtreated. Ideally, those with clinically insignificant prostate cancer should be managed with surveillance. The challenge is to correctly identify such patients and to avoid undertreatment in those with a more aggressive biologic phenotype. The key to such strategies is regular observation, so those patients who manifest more aggressive disease are identified when curative treatment is still feasible. It has been shown that rapid PSA DT in a patient on a watchful-waiting

protocol probably reflects a more aggressive phenotype. However, a number of potential pitfalls exist when analysing PSA DT data from patients on active-surveillance protocols. Significant variability in PSA DT has been demonstrated in such groups. Therefore, surveillance patients should have PSA estimations performed every 3 mo, and they should have a relatively large amount of data available for analysis. The interval on which determination of PSA DT is based must be sufficiently long (6–12 mo) to avoid decisions based on random variations in PSA levels.

In conclusion, analysis of PSA kinetics should play a major role in the management of localised prostate cancer. Comprehensive guidelines for the management of prostate cancer have recently been published by the European Association of Urology [13].

3.2. *Treatment options for localised prostate cancer*

Current management options for localised prostate cancer include radical prostatectomy, external beam radiotherapy or brachytherapy, active surveillance, and hormonal therapy. However, benefits with any of these options have yet to be adequately documented in randomised, controlled trials.

However, there is evidence from one trial, the Scandinavian Prostatic Cancer Group Study Number 4 (SPCG-4), that radical surgery may reduce prostate cancer deaths compared to watchful waiting [14,15]. There was no difference in the rates of overall mortality between the groups, although the mean follow-up of 6 yr may be too short to exclude an effect [15].There is no evidence from randomised controlled trials that radiotherapy is better than watchful waiting [6]. This is also true of external beam radiotherapy or brachytherapy (ie, the insertion of radioactive seeds into the prostate gland).

Mature results from randomised controlled trials in treatment of localised prostate cancer, including SPCG-4 [14,15], the Prostate Cancer Intervention Versus Observation Trial (PIVOT) [16], and the Prostate Testing for Cancer and Treatment (ProtecT) study [17], will not be available for several years.

Existing levels of evidence for active surveillance of patients with low and intermediate risk are discussed below.

3.2.1. *Active surveillance*

Active surveillance is, by definition, an active follow-up, and treatment occurs only if there is evidence of disease progression. This cohort of patients is recognised by having only one or two biopsy cores with cancer, Gleason score $\leq$6, PSA level $\leq$15 ng/ml, PSA density of $\leq$0.2 ng/ml per cubic centimetre, and clinical stage of T1c or T2 [18].

Data from retrospective cohort studies and case series support active surveillance as an appropriate choice in patients with well-differentiated or moderately differentiated, low-volume, prostate cancer who have a life expectancy of $<$10 yr; however, men with higher grade tumours and longer life expectancy may be at excess risk of dying of prostate cancer when managed with active surveillance [3,5,19–22].

This information can be considered in the treatment decision-making process alongside other important factors such as individual patient's values and situation and the potential impact of treatment on the patient's quality of life. The outlook for men with localised prostate cancer can be excellent, and active surveillance can produce survival rates similar to those of more aggressive treatments [3–5,14,19,23]. Screen-detected cancers are mostly of this type.

A prospective phase 2 study of active surveillance with selective delayed intervention was initiated in 1995 [24]. Patients were managed initially with surveillance; those who had a PSA DT $\leq$2 yr, or grade progression on rebiopsy were offered radical intervention; the remaining patients were closely monitored. This cohort consisted of 299 patients with good-risk prostate cancer or intermediate-risk prostate cancer in men $>$70 yr of age. The median PSA DT was 7 yr, and 42% of patients had a PSA DT $>$10 yr. The majority of patients remained on surveillance. At 8 yr, the overall survival rate was 85%, and the disease-specific survival rate was 99%. This study has shown that virtually all men with favourable-risk prostate cancer managed in this fashion will die of unrelated causes. The approaches of active surveillance with selective delayed intervention based on PSA DT and repeat biopsy represent a practical compromise between radical therapy for all patients (which results in overtreatment for patients with indolent disease) and watchful waiting with palliative therapy only (which results in undertreatment for those with aggressive disease) [24,25].

3.2.2. *Radical treatment for localised prostate cancer*

Treatment can cause harm as well as benefit. The principal adverse affects of surgery are sexual dysfunction and incontinence. Surgery can be fatal in 0.1% to 0.3% of cases. Radiotherapy can cause sexual dysfunction, urinary symptoms, and diarrhoea or rectal bleeding (Table 1). Furthermore, there are important potential harms at a population level. These can arise from the diversion of health

Table 1 – Risk of complications following surgery or radiotherapy [5]

Risk	Surgery, %	Radiotherapy, %
Death	0.1–0.3%	<1
Erectile dysfunction 2 yr postoperative	79.6*	6.5
Incontinence	9.6	3.5

* The rate may be as low as 32% with bilateral nerve sparing surgery by experts. It is not known whether this rate can be generally achieved.

care resources from other more effective treatments into an ineffective or poorly performing screening or early detection programme.

Taken together, radical treatment for localised prostate cancer carries more risk in terms of urinary incontinence and impotence than does active surveillance. The policy of radical treatment for all will become harder to sustain as PSA testing becomes more widespread and overdiagnosis leading to overtreatment therefore increases.

4. Conclusions

This article outlines different treatment options across the disease continuum of prostate cancer in terms of localised disease. This information can be considered in the treatment decision-making process alongside other important factors such an individual patient's values and situation and the potential impact of treatment on his quality of life. Taking all of these parameters into consideration, data are presented that support active surveillance as an appropriate choice in patients with well-differentiated or moderately differentiated low-volume prostate cancer who have a life expectancy of <10 yr. However, men with higher grade tumours and longer life expectancy may be at excess risk of death from prostate cancer when managed with active surveillance. The choice between radical treatment and active surveillance is based on evidence of disease progression during initial monitoring, which is estimated from the PSA DT and upgrading at repeat biopsy [18]. Trials investigating long-term outcomes of active surveillance are under way. The hope is that active surveillance will reduce the burden of treatment side- effects without compromising survival.

Looking to the future, translational research aimed at molecular profiling of prostate tumours will lead to better understanding of key pathways and molecular events that include better prognostic markers to select patients suitable for active surveillance from aggressive tumours that are candidates for radical treatment.

Conflicts of interest

The author has nothing to disclose.

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