

Active surveillance vs radical prostatectomy

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INTRODUCTION

Prostate cancer is a major cause of death among men in European countries, with nearly 202 100 cases and 68 200 deaths in the European Union in 2004 [1]. The incidence varies considerably among countries and appears to be increasing because of more frequent and better diagnostic tests, an ageing population, and probably a true increase in the occurrence of the disease [2]. There are no obvious strategies for prevention, so screening and early detection have been considered as possible interventions to reduce the number of deaths [3].

The increase in the incidence of prostate cancer raises the possibility that many cases detected by PSA testing are over-treated, i.e. many patients might not become symptomatic despite being left untreated. The challenge of managing early prostate cancer is to differentiate patients with clinically relevant cancers from those whose 'disease' is destined to be merely an incidental histological phenomenon.

THE NATURAL HISTORY OF PROSTATE CANCER AND DIAGNOSTIC TESTS

The natural history of prostate cancer is not fully established, but it is well known that the disease is often indolent. It is slow growing in many cases, and there is a long phase during which it remains undiscovered. This long latent phase is potentially advantageous for screening, but it appears that some tumours are very slow growing and might never become clinically important [4,5]. Men with such tumours often die from another cause [6]. Although the outcome varies strongly with age at diagnosis and with Gleason score, it is interesting that the predicted 15-year prostate cancer mortality rate in men with Gleason score 2–4 cancer is 4–7%, compared with 27–73% mortality from other causes [6]. The mortality rate in men with localized tumours is little different from that in other men [6,7]. The relatively benign course of many tumours means that, in most cases, the

benefits of treatment might not outweigh its side-effects.

There are, in principle, two tests that can be used in mass screening, i.e. PSA assay and a DRE. The PSA test is simple, cheap, safe and acceptable, but prostate biopsy, which is 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 [8]. There is no good standard against which to test it, because prostate biopsy itself can miss 10–30% of cases. Also, biopsies are not normally taken in men with a negative PSA test, so it is difficult to assess the number of false-negative tests and thus 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, the PSA test is not specific for clinically important disease. DRE is less acceptable and less accurate (i.e. has lower sensitivity and specificity) than PSA testing [8]. Comprehensive guidelines for managing prostate cancer were recently published by the European Association of Urology (available online at www.uroweb.org).

TREATMENT OPTIONS FOR LOCALIZED PROSTATE CANCER

Current management options for localized prostate cancer include radical prostatectomy (RP), external beam radiotherapy or brachytherapy (the insertion of radioactive seeds into the prostate gland), active surveillance, and hormone therapy. However, the benefits of these options have yet to be adequately documented in randomized controlled trials.

There is evidence from one trial, the fourth Scandinavian Prostatic Cancer Group study (SPCG-4) [9], that compared with watchful waiting, radical surgery might reduce prostate cancer deaths; at 10 years there were fewer deaths among men who had had RP than among those who underwent watchful waiting (relative risk 0.56, $P=0.01$) [10]. At a median follow-up of 8.2 years there was a

small but significant ($P=0.04$) reduction in the 10-year overall mortality rate in the RP group (relative risk 0.74) [10]. In addition, a significant reduction in the risk of distant metastases emerged at 10 years (relative risk 0.60, $P=0.004$). There is no evidence from randomized controlled trials that radiotherapy is better than watchful waiting [8]. The same is true for external beam radiotherapy and brachytherapy.

Several years will elapse before mature results are available from randomized controlled trials of the treatment of localized prostate cancer, including the SPCG-4, the Prostate Cancer Intervention Versus Observation Trial [11], and the Prostate Testing for Cancer and Treatment study [12]. Evidence of the benefit of active surveillance in low- and intermediate-risk patients is discussed below.

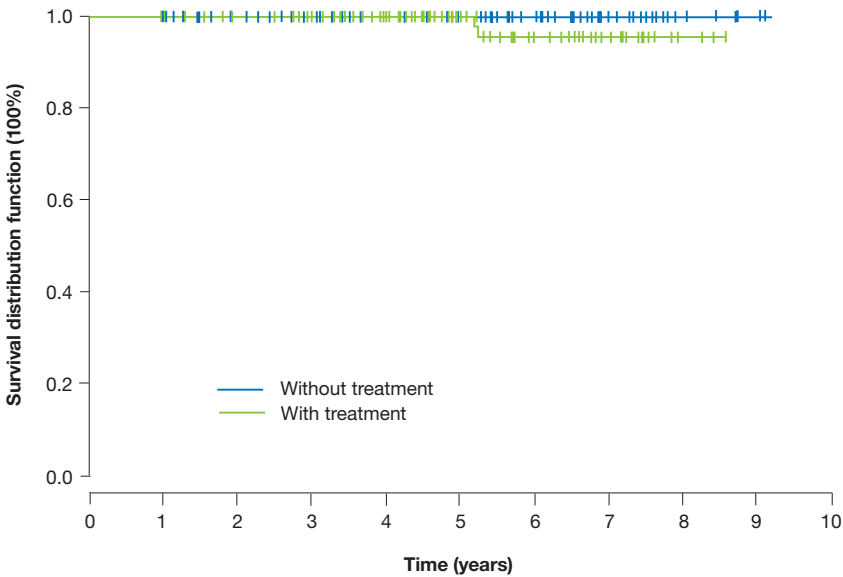
ACTIVE SURVEILLANCE

Active surveillance comprises active monitoring, with tailored treatment only if there is evidence of disease progression. Suitable patients have only one or two biopsy cores with cancer, Gleason score ≤ 6 , a PSA level of ≤ 15 ng/mL, a PSA density of <0.2 ng/mL/cm³, and clinical stage T1c or T2 [13].

Data from retrospective cohort studies and case series support active surveillance as an appropriate choice in patients with well or moderately differentiated, low-volume prostate cancer who have a life-expectancy of <10 years. However, men with higher-grade tumours and longer life-expectancy might be at excess risk of death from prostate cancer managed with active surveillance [5–7,14–16]. This information can be considered with other important factors, e.g. the individual patient's values and situation, and the potential impact of treatment on his quality of life, in the treatment decision-making process.

The prognosis for men with localized prostate cancer can be excellent, and active surveillance can achieve survival rates similar to those of more aggressive treatment

FIG. 1. The disease-specific survival in patients with low-risk prostate cancer was 99%. Only two of 299 patients had died from prostate cancer at 8.5 years of follow-up; each of these two died 5 years after study enrolment, and each had a PSA doubling time of <2 years. Data from Klotz [18].



sexual dysfunction and incontinence. Surgery is fatal in $\approx 0.5\%$ of cases [20,21], and radiotherapy can cause sexual dysfunction, urinary symptoms and diarrhoea or rectal bleeding (Table 1) [20–23]. Furthermore, there are important potential harms at the population level. These harms can arise from the diversion of healthcare resources from other, more effective treatments towards an ineffective or poorly performed screening or early detection programme.

CONCLUSION

In this review I outlined the different treatment options in localized prostate cancer. This information can be considered with other important factors, e.g. the individual patient's values and situation and the potential impact of treatment on his quality of life, in the treatment decision-making process. Taking all of these factors into consideration, the data support active surveillance as an appropriate choice in patients with well or moderately differentiated, low-volume prostate cancer who have a life-expectancy of <10 years. Men with higher-grade tumours and longer life-expectancy might be at excess risk of death from prostate cancer managed with active surveillance.

In the future, translational research aimed at identifying the molecular profiles of prostate tumours will lead to a better understanding of the key pathways and molecular events leading to prostate cancer, and to the identification of better prognostic markers to select patients who are suitable for active surveillance vs those with aggressive tumours who are candidates for radical treatment.

CONFLICTS OF INTERESTS

The author has declared no conflicts of interests.

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Risk	Surgery, %	Radiotherapy, %	TABLE 1 The risk of complications after surgery or radiotherapy for prostate cancer. Adapted with permission from Slaughter et al. [22]
Death	0.48*	<1	
Erectile dysfunction 2 years after surgery	0.37–0.56†	61.5	
Incontinence	9.6	3.5	

Data from *Alibhai et al. [20]; †Lu-Yao et al. [21]. ‡The risk might be as low as 32% with bilateral nerve-sparing surgery by experts [23]. It is not known whether this rate can be generally achieved.

[5–7,9,14,17]. Screen-detected cancers are mostly of this type.

A prospective phase II study of active surveillance with selective delayed intervention was initiated in 1995 [18,19]. Management was initially surveillance; patients who had a PSA doubling time of ≤ 2 years or had a grade progression on re-biopsy were offered radical intervention. The remaining patients were closely monitored. The cohort comprised 299 patients aged ≥ 70 years who had low-risk prostate cancer (PSA level <10 ng/mL, Gleason score < 6 , or stage T <2a) or intermediate-risk prostate cancer (PSA 10–20 ng/mL, Gleason score 7, or stage T2b/c). The median PSA doubling time was 7 years, and 42% of the cohort had a PSA doubling time of >10 years. Most patients remain on surveillance. At 8 years the overall

actuarial survival was 85%, and the disease-specific survival 99% (Fig. 1). To date, this study has shown that almost all men with low-risk prostate cancer managed in this manner will die from unrelated causes. The approach of active surveillance with selective delayed intervention based on PSA doubling time and repeat biopsy represents a practical compromise between radical therapy for all patients (which results in over-treatment of indolent disease) and watchful waiting with palliative therapy only (which results in under-treatment of aggressive disease).

RADICAL TREATMENT OF LOCALIZED PROSTATE CANCER

Radical treatment (surgery or radiotherapy) can be harmful as well as beneficial. The principal adverse events after surgery are

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Abbreviations: SPCG, Scandinavian Prostatic Cancer Group; RP, radical prostatectomy.