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# Active surveillance versus 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 EU in 2004.<sup>1</sup> The incidence varies considerably between 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.<sup>2</sup> There are no obvious strategies for prevention, so screening and early detection have been considered as possible interventions to reduce the number of deaths.<sup>3</sup>

The increase in the incidence of prostate cancer raises the possibility that many cases detected by PSA testing are over-treated. In other words, many patients may 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. It is well known, however, 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 may never become clinically important.<sup>4,5</sup> Men with such tumours often die from another cause.<sup>6</sup> 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 approximately 4–7%, compared with 27–73% mortality from other causes.<sup>6</sup> The mortality rate in men with very localized tumours is little different from that in other men.<sup>6,7</sup> 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 may be used in mass screening: PSA and DRE. The PSA test is simple, cheap, safe, and acceptable. However, 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.<sup>8</sup> There is no good standard against which to test it, because prostate biopsy itself may miss 10–30% of cases. Also, biopsies are not normally performed on 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.<sup>8</sup>

Comprehensive guidelines for the management of prostate cancer were recently published by the European Association of Urology (available online at [www.uroweb.org](http://www.uroweb.org)).

### **Treatment options for localized prostate cancer**

Current management options for localized prostate cancer include radical prostatectomy, 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),<sup>9</sup> that compared with watchful waiting, radical surgery may reduce prostate cancer deaths: at 10 years, there were fewer deaths among men who had undergone radical prostatectomy than among those who had undergone watchful waiting (relative risk 0.56,  $P = 0.01$ ).<sup>10</sup> 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 radical prostatectomy group (relative risk 0.74).<sup>10</sup> 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.<sup>8</sup> The same is true for external beam radiotherapy and brachytherapy.

Several years will elapse before mature results are available from randomized controlled trials of treatment of localized prostate cancer, including the SPCG-4, the Prostate Cancer Intervention Versus Observation Trial,<sup>11</sup> and the Prostate Testing for Cancer and Treatment study.<sup>12</sup>

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 or less, PSA 15 ng/mL or less, PSA density less than 0.2 ng/mL/cm<sup>3</sup>, and clinical stage T1c or T2.<sup>13</sup>

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 less than 10 years. However, men with higher-grade tumours and longer life expectancy may be at excess risk of death from prostate cancer managed with active surveillance.<sup>5-7,14-16</sup> This information can be considered alongside other important factors, such as 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.<sup>5-7,9,14,17</sup> Screen-detected cancers are mostly of this type.

A prospective phase II study of active surveillance with selective delayed intervention was initiated in 1995.<sup>18,19</sup> Management was initially surveillance; patients who had a PSA doubling time of 2 years or less 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 or more who had low-risk prostate cancer (PSA < 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 more than 10 years. Most patients remain on surveillance. At 8 years, the overall actuarial survival is 85%, and the disease-specific survival is 99% (Fig. 1). To date, this study has shown that almost all men with low-risk prostate cancer managed in this manner will die of 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 following surgery are sexual dysfunction and incontinence. Surgery is fatal in approximately 0.5% of cases,<sup>20,21</sup> and radiotherapy can cause sexual dysfunction, urinary symptoms, and diarrhoea or rectal bleeding (Table 1). Furthermore, there are important potential harms at the population level. These harms can arise from the diversion of health-care resources from other, more

effective treatments towards an ineffective or poorly performed screening or early detection programme.

## **Conclusion**

This review has outlined the different treatment options in localized prostate cancer. This information can be considered alongside other important factors, such as 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 less than 10 years. Men with higher-grade tumours and longer life expectancy may 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 versus those with aggressive tumours who are candidates for radical treatment.

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Abbreviation: **SPCG**, Scandinavian Prostatic Cancer Group.

TABLE 1 Risk of complications following surgery or radiotherapy. (Adapted with permission from Slaughter, *et al.*,<sup>22</sup> Institute for Clinical Evaluative Sciences, Toronto, Canada.)

Risk	Surgery (%)	Radiotherapy (%)
Death	0.48* 0.37–0.56 <sup>†</sup>	< 1
Erectile dysfunction 2 years after surgery	79.6 <sup>‡</sup>	61.5
Incontinence	9.6	3.5

\*Data from Alibhai, *et al.*<sup>20</sup>

<sup>†</sup>Data from Lu-Yao, *et al.*<sup>21</sup>

<sup>‡</sup>The risk may be as low as 32% with bilateral nerve sparing surgery by experts.<sup>23</sup> It is not known whether this rate can be generally achieved.

FIG. 1. Disease-specific survival in low-risk prostate cancer patients was 99%. Only two of 299 patients had died of prostate cancer at 8.5 years of follow-up. Each of these two patients died 5 years after study enrolment, and each had a PSA doubling time of less than 2 years. (Data from Klotz.<sup>18</sup>)

