

# Active surveillance: towards a new paradigm in the management of early prostate cancer

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Prostate cancer is the only human cancer that is curable but which commonly does not need to be cured. Active surveillance is a new strategy that aims to individualise therapy by selecting only those men with significant cancers for curative therapy. Patients with favourable tumour characteristics are closely monitored using serum prostate specific antigen (PSA) concentrations and repeat prostate biopsies. The choice between radical treatment and continued observation is based on evidence of disease progression, defined in terms of the PSA doubling time, and “upgrading” at repeat biopsy. Active surveillance provides an excellent opportunity for studies to identify markers of prostate-cancer behaviour. Knowledge of prostate cancer biomarkers would have an immediate effect on clinical decision-making and would also identify targets for the development of novel therapeutic strategies. In the longer term, active surveillance may accelerate progress towards a new treatment paradigm for early prostate cancer based on the selective use of therapies designed, not to eradicate the disease, but to alter its natural history.

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The annual incidence of prostate cancer in the USA has more than doubled since the introduction of the prostate specific antigen (PSA) test (figure 1). This rise is consistent with the possibility that most PSA-screen-detected cases are overdiagnosed; that is, even without treatment, they would not have become symptomatic.<sup>1</sup> However, prostate cancer is by no means a uniformly indolent condition, being responsible for 3% of all male deaths in the USA (figure 2).<sup>2</sup> The challenge of managing early prostate cancer is to distinguish patients with clinically relevant cancers from those whose “disease” is destined merely to be an incidental histological event. At present, we cannot accurately predict prostate-cancer behaviour in an individual, so a standard approach is to offer curative treatment to all men with localised disease, while acknowledging that this treatment is unnecessary in most cases. This approach is far from ideal, not least because of the significant risks of urinary incontinence and impotence associated with such treatment. This policy of radical treatment for all will become harder to sustain as PSA testing becomes more widespread, and overdiagnosis therefore increases.

Active surveillance is an alternative strategy, which aims to individualise therapy by selecting only those men with significant cancers for curative therapy. Patients are closely monitored using serum PSA concentrations and repeat prostate biopsies. The choice between radical treatment and

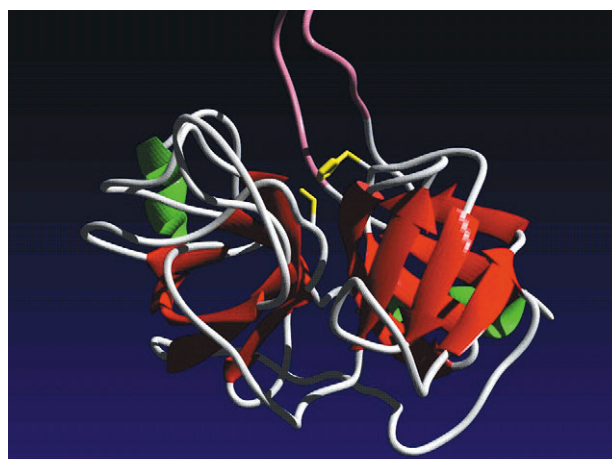


Figure 1. Ribbon structure of prostate specific antigen.

Courtesy of Paul Bamford

observation is based on evidence of disease progression, defined in terms of the PSA doubling time (PSADT), and “upgrading” at repeat biopsy. There are no long-term outcome data for active surveillance but the hope is that, compared with a policy of immediate radical treatment in all cases, surveillance will reduce the burden of treatment side-effects without compromising survival.

## Rationale for active surveillance of early prostate cancer

### Some men benefit from radical treatment

Prostate cancer, unlike cancers of other sites, often has a very indolent natural history. Whereas patients with any other curable cancer would automatically be offered radical treatment, “watchful waiting” has been a recognised approach to managing prostate cancer, with acceptable results in selected patients.<sup>3</sup> In fact, the first good evidence that some men benefit from radical treatment of localised prostate cancer has only recently become available. From 1989 to 1999, the Scandinavian Prostatic Cancer Group Study randomised almost 700 men with localised disease between radical prostatectomy and watchful waiting.<sup>4</sup> At 8 years, the risk of metastatic disease was 13% versus 27% in men randomised to surgery and watchful waiting, respectively ( $p=0.03$ ). This is an important endpoint, and no doubt will translate in time to an overall survival benefit

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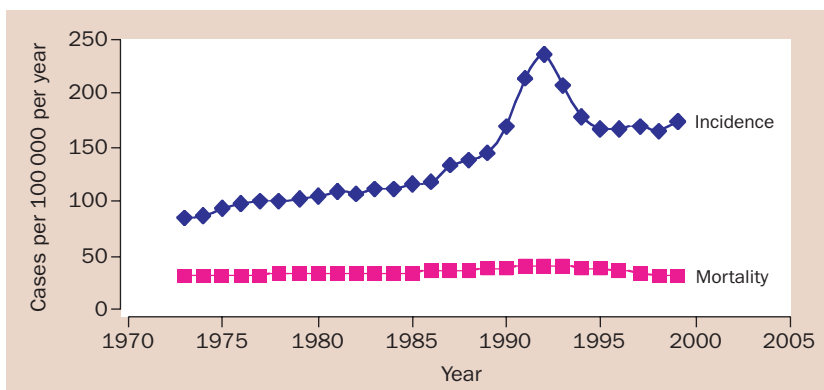


Figure 2. Temporal trends in prostate-cancer incidence and mortality in the USA.

for those receiving radical treatment. In the light of these results, it is no longer possible to argue that watchful waiting is the appropriate management for all men with localised prostate cancer. Since we know that some men benefit from radical treatment, the question now is which men benefit?

#### Most men will not benefit from radical treatment

The improvement in the risk of metastatic disease achieved by surgery was large in the Scandinavian study. Just seven men needed to be treated for one to benefit. However, these results may not be generalisable to the contemporary management of early prostate cancer. In particular, patients with PSA-screen-detected disease will have a much more favourable outcome, even without treatment, than those diagnosed clinically in Scandinavia in the late 1980s and early 1990s. It is estimated that a PSA screening programme will detect prostate cancers an average of 9 years before clinical diagnosis in the absence of screening.<sup>5</sup> Furthermore, given the often slow natural history of the disease, together with the typical age distribution, early detection using PSA testing risks overdiagnosis; that is death from other causes before the cancer would have become symptomatic. The proportion of cases identified by PSA screening that are overdiagnosed is difficult to establish, and estimates vary between 29% and 84%.<sup>6,7</sup>

The reported geographical variation in prostate cancer incidence provides one indication of the frequency of overdiagnosis. In countries such as Denmark, where PSA screening is uncommon, the estimated age-standardised annual incidence rate for the year 2000 is 31 per 100 000, whereas in the USA, where PSA screening is widespread, the incidence is 104 per 100 000.<sup>8</sup> If one assumes that there is no difference in the “real” incidence between these countries, it would suggest that 70% (73/104) of prostate cancers in the USA are overdiagnosed. While current data do not provide an accurate estimate of the risk of overdiagnosis, it is clear that a significant proportion of men with early prostate cancer would never develop symptomatic disease, even without treatment.

PSA-screen-detected prostate cancers have only become common in the past 10 years or so, and the long-term results of watchful waiting for such cancers are not known. Given the lead time bias and the risk of overdiagnosis, the

outcome will certainly be more favourable than that of watchful waiting for clinically diagnosed cancers. Nicholson and Harland,<sup>9</sup> using the mature outcome data of watchful waiting from the pre-PSA era, together with temporal trends in incidence and mortality since the introduction of PSA testing, have modelled the expected 15-year mortality associated with watchful waiting for screen detected cancers (figure 3). While the outcome varies both with age at diagnosis and with Gleason score, it is interesting to note

that the predicted 15-year prostate cancer mortality for men with Gleason score-6 cancers is 10% or less, compared with a mortality of 40–76% from other causes. These considerations strongly suggest that a policy of immediate radical treatment for all screen-detected cases will, at best, have only a small effect on overall survival. Most men with screen-detected early prostate cancers are destined to die from causes other than prostate cancer. Radical treatment of their prostate cancer may not improve their longevity, but it can have a big effect on their lifestyle.

#### Morbidity of radical treatment

Overdiagnosis of prostate cancer would not matter if treatment had no morbidity. It would be acceptable, albeit costly, to treat all cases, including those destined never to cause symptoms, if treatment was without problems. However, the side-effects of radical prostatectomy and of radical radiotherapy can be considerable. For example, in the Scandinavian study of radical prostatectomy versus

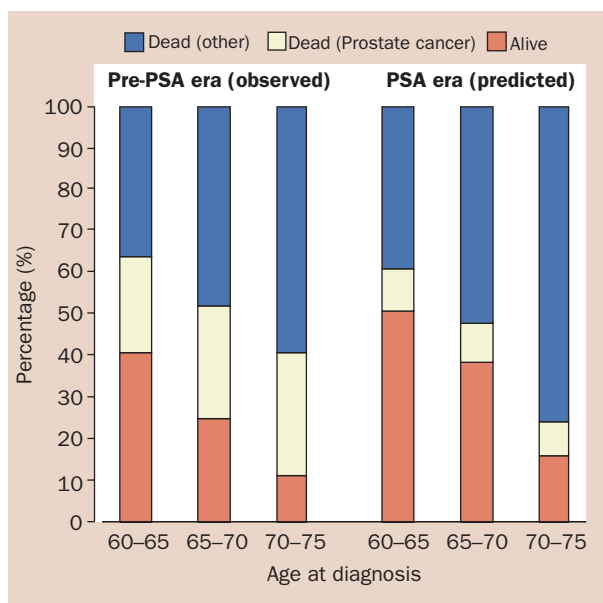


Figure 3. Effect of PSA screening on the 15-year outcome of watchful waiting for localised prostate cancer, with a Gleason score of 6. The pre-PSA era data are those reported by Albertsen,<sup>3</sup> while the data from the PSA era are those modelled by Nicholson and Harland.<sup>9</sup>

watchful waiting, men randomised to surgery had significantly increased rates of urinary incontinence (49% vs 21%) and of impotence (80% vs 45%).<sup>10</sup> Figures such as these highlight the fact that treatment for prostate cancer can substantially affect a man's lifestyle, and intervention should be restricted to those who need it.

### The problem of predicting individual cancer behaviour

Accurate prediction of the natural history of individual cases of prostate cancer would enable radical treatment to be targeted to those men who could benefit from it, while sparing the remainder the risks of treatment side-effects. The established prognostic factors, such as Gleason score, PSA concentration, and T stage, are of some use. For example, the benefits of radical treatment of localised prostate cancer seem to be greater in those cases with a higher Gleason score: a recent Mayo Clinic analysis<sup>11</sup> of long-term outcome after radical prostatectomy was designed to be as comparable as possible with the watchful waiting series reported by Albertsen.<sup>3</sup> Both were based on about 750 men with clinically localised disease, aged between 55 and 74, who were diagnosed between 1971 and 1984. The outcome in terms of 15-year mortality from prostate cancer was derived using the same competing risks methodology, and is shown for men aged between 60 and 64 at diagnosis in figure 4. While there are likely to be systematic biases between the two data sets, and while the outcomes for PSA-screen-detected cases will be much better than these figures, nonetheless, these data suggest that the benefit of radical treatment is greater for higher Gleason scores. Although the established prognostic factors can be useful in this way, they explain only a small proportion of the variation in prostate cancer behaviour.<sup>12</sup> There is a pressing need for better ways of selecting which men stand to benefit from radical treatment.

### Active surveillance: a selective approach to radical treatment of prostate cancer

The aim of active surveillance of early prostate cancer is to individualise therapy by selecting only those men with significant cancers for curative therapy. Patients with favourable tumour characteristics in terms of T stage, Gleason score, and PSA concentration are closely monitored using serum PSA concentrations and repeat prostate biopsies. The choice between radical treatment and continued observation is based on evidence of disease progression, with progression defined in terms of the PSADT, and "upgrading" at repeat biopsy. The aim is to identify cases for treatment long before any symptoms or overt clinical signs of tumour progression are evident. The use of PSADT to guide management is based on the knowledge that preoperative serum PSA concentrations correlate significantly with the volume of prostate

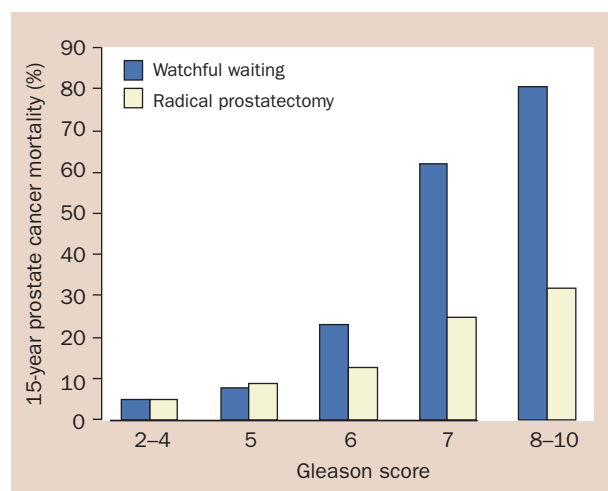


Figure 4. 15-year prostate cancer mortality, using competing risks analysis, for men aged 60–64 at diagnosis: comparison of Mayo Clinic radical prostatectomy series<sup>10</sup> with Albertsen watchful waiting data.<sup>3</sup>

cancer in radical prostatectomy specimens,<sup>13</sup> together with the finding that temporal PSA trends in untreated patients conform to an exponential model, suggesting that PSADT is constant over time for a given patient.<sup>14</sup> It seems intuitive that PSADT will approximate to the rate of tumour growth. In support, PSADT is well established as an important predictor of the risk of metastatic disease<sup>15</sup> and survival<sup>16</sup> in men with PSA failure after radical treatment, and, in a report of 113 men on watchful waiting, McLaren et al<sup>17</sup> reported PSADT to be the strongest predictor of clinical progression.

Active surveillance must be distinguished from watchful waiting, which for decades has described a policy of observation with the use of palliative treatment for symptomatic progression. Put another way, to emphasise the differences between these two contrasting approaches, watchful waiting involves relatively lax observation with late, palliative treatment for those who develop symptoms of progressive disease, and active surveillance involves close monitoring with early, radical treatment in those with signs of progression (see table).

### Preliminary outcome data for active surveillance

The concept of active surveillance was formally described for the first time in 2001 by Richard Choo, in a report of the

#### Contrasts between active surveillance and watchful waiting

	Active surveillance	Watchful waiting
Aim	To individualise treatment	To avoid treatment
Patient characteristics	Fit for radical treatment Age 50–80	Age >70 or life expectancy <15 yrs
Tumour characteristics	T1–T2 GS ≤7 Initial PSA <15	Any T stage GS ≤7 Any PSA
Monitoring	Frequent PSA testing Repeat biopsies	PSA testing unimportant No repeat biopsies
Indications for treatment	Short PSADT Upgrading on biopsy	Symptomatic progression
Treatment timing	Early	Delayed
Treatment intent	Radical	Palliative

preliminary findings from a prospective single-arm study, started in 1995, of a "watchful observation protocol with selective delayed intervention for clinical, histologic, or PSA progression".<sup>18</sup> Eligibility was restricted to men with untreated, localised, favourable-grade prostate adenocarcinoma (T1b–T2b N0 M0, Gleason score  $\leq 7$ , and PSA  $\leq 15$  ng/mL). Men were seen every 3 months for the first 2 years and then at 6-month intervals, with digital rectal examination and PSA testing on each visit. PSADT was estimated from a linear regression of  $\ln(\text{PSA})$  against time. Repeat prostate biopsy took place at 18 months. Indications for treatment were PSA progression, defined as a PSADT of  $< 2$  years and a final PSA of  $> 8$  ng/mL; histological progression, defined as upgrading to Gleason score of 8 or more on re-biopsy; or clinical progression. By the time of the latest update,<sup>19</sup> 206 men had entered the study. They ranged in age from 49–84 with a median of 70 years. Median initial PSA was 6.5 ng/mL. 163 patients (79%) had a biopsy Gleason score of 6 or less, and 130 (64%) had a stage T1 tumour. At a median follow-up of 29 months, 137 men remain on observation within the surveillance programme, 48 have received radical treatment, 17 have changed to a watchful waiting programme (ie, no longer appropriate for radical treatment) and four have died of unrelated causes. Of the 48 men who have had radical treatment, 29 had met the criteria for disease progression, while the other 19 elected or were advised to have treatment without having met the criteria. The actuarial probability of freedom from disease progression was 67% ( $\pm 12\%$ ) at 4 years, suggesting that up to two-thirds of men could be spared radical treatment with this protocol. Of note, 42% of cases had a PSADT of 10 years or more, suggesting a particularly indolent course in these patients.

A different surveillance policy, based largely on repeat biopsies, has been described by Carter et al.<sup>20</sup> 81 men with a median age of 65 years who had T1c disease, a PSA density of less than 0.15 ng/mL/cm<sup>3</sup>, and favourable needle biopsy findings (defined as Gleason score  $\leq 6$ , no Gleason grade 4 or 5 cancer, fewer than 3 cores involved, and less than 50% of any one core involved) were followed with PSA and digital rectal examination at 6-monthly intervals, and annual prostate biopsies. Radical treatment was recommended for disease progression defined as unfavourable repeat biopsy findings (Gleason score of 4 or 5, greater than 2 biopsy cores involved, greater than 50% involvement of any core). At a median follow-up of 23 months, 25 (31%) had disease progression. These two reports indicate the feasibility of an active surveillance policy, although the short-term outcome data presented must be regarded as preliminary and longer-term outcomes, including prostate cancer mortality, are awaited with interest.

#### **Optimising the active surveillance protocol**

Comparison of these two reports of active surveillance shows that there is no consensus on the criteria used to define disease progression requiring radical treatment. In particular, the Carter criteria are based on the results of

repeat biopsies alone,<sup>19</sup> whereas Choo and colleagues also use PSADT and clinical criteria.<sup>17</sup> Although both groups use repeat biopsies, they differ with respect to the frequency of the procedure and the findings that merit intervention. At present there is insufficient evidence to establish an optimum active surveillance protocol. However, some general points can be made. Initial analyses have shown that the variation in findings between initial and repeat biopsies, at least within the first few years of surveillance, indicate the limitations of sampling, rather than tumour evolution.<sup>21,22</sup> That is, cancers are downgraded on repeat biopsy as often as they are upgraded. If one accepts the presence of high-grade cancer as an indication for radical treatment, then there is an argument for a more extensive initial biopsy procedure with at least, say, 12 needle cores to minimise sampling error. If initial sampling error can be reduced in this way, subsequent repeat biopsies could be less frequent.

If PSADT is a potentially useful measure of the rate of cancer progression, what is the appropriate cut-off point to use as an indication for radical treatment? Once again, it is not possible to make an evidence-based recommendation. The choice of PSADT cut-off point is necessarily somewhat arbitrary. A shorter cut-off point will spare more men the side-effects of radical treatment, but if the cut-off point is too short one might merely be identifying those men who already have metastatic disease. On the other hand, a longer cut-off point, while making it more likely that men who stand to benefit from radical intervention will be treated appropriately, necessarily means that fewer men are spared treatment side-effects. The policy at the Royal Marsden Hospital, London, UK, is to use an individualised cut-off point for each patient, depending on absolute PSA concentration and life expectancy (from actuarial tables), and to assume that low-grade prostate cancer seldom becomes symptomatic before the serum PSA concentration reaches 50 ng/mL. For example, a man with a PSA concentration of 6 ng/mL needs three PSA doublings before his PSA will reach 50 ng/mL. If his life expectancy is 10 years, then his PSADT cut-off point will be around 3 years. On the other hand, if his life expectancy was 20 years, then a cut-off point of 7 years would be more appropriate. In practice, the choice of PSADT cut-off point is an exercise in shared decision-making, and is affected by the relative importance that the patient places on treatment side-effects versus possible improvements in longevity.

Another issue related to the use of PSADT as an indication for treatment relates to the uncertainty as to the number of PSA measurements, and the duration of PSA monitoring, needed before one can confidently estimate an individual's "true" PSADT. Gerber et al,<sup>23</sup> in a study of 37 men managed by watchful waiting, reported a poor correlation between initial PSADT, calculated in the first 9 months after diagnosis, with overall PSADT using all available values (Pearson correlation coefficient 0.42). However, PSA testing took place at 6-month intervals, and it is possible that with more frequent testing, the strength of this correlation would improve.<sup>24</sup> A continuing study at the Royal Marsden, Hospital using monthly PSA concentrations obtained from men on active surveillance,

aims to establish the optimum frequency of PSA testing, and the number of findings needed to make an accurate estimate of long term PSADT. This is an important issue because the aim of active surveillance is to identify as soon as possible those cases that will require treatment, at such a time when that treatment will still be curative.

### Potential of active surveillance for early prostate cancer

Active surveillance may allow two-thirds of men with early prostate cancer to be spared the side-effects of treatment, without compromising their survival. This is an attractive prospect, not just for patients, but also for health economists, because it would save valuable resources that are currently spent on “unnecessary” radical treatment. While the initial experience with active surveillance indicates its feasibility, long-term outcome data will be required to establish its effectiveness. A randomised study of active surveillance versus immediate radical treatment, the ProtecT study, is underway in the north of England, and a similar study is planned by the National Cancer Institute of Canada.

Active surveillance may prove to be not just an attractive alternative to immediate radical treatment, but also a step towards a new paradigm for prostate cancer management. Active surveillance provides an ideal opportunity for us to improve our understanding of the basis for the extraordinary variation in prostate cancer behaviour. If patients receive immediate radical treatment, only 15–25% of them will develop recurrence, which typically is detected years later. Long-term follow-up of large numbers is therefore needed to obtain outcome data to assess the use of candidate biomarkers, and it is impossible to distinguish insignificant cancers from those that were significant but were treated successfully. By contrast, outcome in terms of PSADT is available for all men on active surveillance within a matter of months, so that candidate biomarkers can be assessed rapidly in a modest number of patients. At the Royal Marsden Hospital and the Institute of Cancer Research, together with our collaborators, we are studying the relation between PSADT and potential markers of prostate-cancer behaviour, including tumour gene expression profiles, serum proteomics, tumour oxygenation, cytokine profiles, and functional imaging. A better understanding of the determinants of prostate cancer behaviour would not only enable us to identify which cases needed treatment but, perhaps more importantly, would also indicate potential targets for the development of novel therapeutic strategies.

Active surveillance could also provide an attractive setting for the assessment of therapeutic agents. Cancer prevention trials typically require tens of thousands of healthy subjects, at low risk of developing cancer, followed up for decades. Men with early prostate cancer on active surveillance could take part in trials of prevention strategies, with the aim being the prevention of clinically significant disease. Prevention strategies could be rapidly tested in small numbers of patients, with early endpoints based on PSADT, functional imaging, and repeat biopsies. This novel

### Search strategy and selection criteria

Published data for this article were identified by a MEDLINE search with combinations of the search terms: “prostatic neoplasms”, “watchful waiting”, and “conservative management”. References from relevant articles, and the author’s personal collection were also included. Only articles published in English in the PSA era (since 1990) were considered. Papers were selected if they included clinical outcome data from patients with localised prostate cancer managed conservatively, but with radical intent.

approach to clinical trials could accelerate progress towards a future in which the management of early prostate cancer was based on observation, with the selective use of therapies designed, not to eradicate the disease, but to alter its natural history.

### Conclusions

Active surveillance may spare two-thirds of men with early prostate cancer the side-effects of treatment, without compromising their survival. Continuing studies seek to identify the optimum schedule of PSA testing and repeat biopsies, the appropriate indications for intervention, and the long-term efficacy of surveillance in comparison with immediate radical treatment. Active surveillance provides excellent opportunities to identify markers of prostate cancer behaviour, and to test novel therapeutic strategies. Active surveillance may prove to be the start of a paradigm-shift in the management of early prostate cancer.

### Conflict of interest

None declared.

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