Early outcomes of active surveillance for localized prostate cancer

CLAIRE HARDIE, CHRIS PARKER, ANDREW NORMAN*, ROS EELES, ALAN HORWICH, ROBERT HUDDART and DAVID DEARNALEY

*Academic Unit of Radiotherapy & Oncology and *Department of Computing and Information, The Royal Marsden NHS Trust and Institute of Cancer Research, Sutton, Surrey, UK*

Accepted for publication 13 December 2004

OBJECTIVE

To describe the preliminary clinical outcomes of active surveillance (AS), a new strategy aiming to individualize the management of early prostate cancer by selecting only those men with significant cancers for curative therapy, and illustrate the contrast with a policy of watchful waiting (WW).

PATIENTS AND METHODS

Eighty men with early prostate cancer began AS at the authors' institution between 1993 and 2002. Eligibility included histologically confirmed prostatic adenocarcinoma, fitness for radical treatment, clinical stage T1/T2, N0/X, M0/X, a prostate specific antigen (PSA) level of ≤20 ng/mL, and a Gleason score of ≤7. PSA was measured and a digital rectal examination conducted at 3–6 month intervals. The decision between continued monitoring or radical treatment was informed by the rate of rise of PSA, and was made according to the judgement of each patient and clinician. During the same period, 32 men with localized prostate cancer (any T stage, N0/X, M0/X, any PSA, Gleason score ≤7) were managed by WW; hormonal treatment was indicated for symptomatic prostate cancer progression. The PSA doubling time (DT) was calculated using linear regression of ln(PSA) against time, using all pretreatment PSA values.

RESULTS

At a median follow-up of 42 months, 64 (80%) of the 80 patients on AS remained under observation, 11 (14%) received radical treatment and five (6%) died from other causes. No patient developed evidence of metastatic disease, none started palliative hormone therapy, and there were no deaths from prostate cancer. Of the 11 patients who received radical treatment all remained biochemically controlled with no clinical evidence of recurrent disease. The median PSA DT while on AS was 12 years. Twenty (62%) of the 32 patients on WW remained on observation, eight (25%) received palliative hormonal therapy and four (12%) died, including one from prostate cancer.

CONCLUSIONS

AS is feasible in selected men with early prostate cancer. The natural history of this disease often appears extremely indolent, and most men on AS will avoid radical treatment. There is a marked contrast between AS (with radical treatment for biochemical progression) and WW (with palliative treatment for symptomatic progression). Ongoing studies are seeking to optimize the AS protocol, and to compare the long-term outcomes with those of immediate radical treatment.

KEYWORDS

prostate cancer, active surveillance, watchful waiting, outcome, treatment protocol

INTRODUCTION

Prostate cancer is the only human cancer which is curable but which commonly does not need to be cured. It is estimated that 50–80% of all cancers detected by PSA screening are over-diagnosed [1], i.e. even with no treatment they would not have become symptomatic. However, prostate cancer is by no means a uniformly indolent condition, being responsible for >9000 deaths a year in the UK. 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 phenomenon. At present, it is not possible to accurately predict cancer behaviour in an individual, so a standard approach is to offer curative treatment to all men with localized disease, whilst acknowledging that this treatment is 'unnecessary' in most. 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 over-diagnosis therefore increases.

Active surveillance (AS) is an alternative strategy that aims to individualize therapy by selecting only those men with significant cancers for curative therapy [2]. Patients are closely monitored using serum PSA levels with or without repeat prostate biopsies. The choice between radical treatment and observation is based on evidence of disease progression defined in terms of the PSA doubling time (PSADT) or 'upgrading' at repeat biopsy. AS aims to reduce the burden of treatment side-effects without compromising survival. It must be distinguished from 'watchful waiting' (WW), which for decades has described a policy of observation with the use of palliative treatment for symptomatic progression. Whereas WW involves relatively lax observation with late, palliative hormonal treatment for those who develop symptoms of progressive disease, AS involves close monitoring with early, radical treatment in those with signs of progression.

  doi:10.1111/j.1464-410X.2005.05446.x

Variable	AS	WW
Median (range) age, years	70.5 (59–81)	77 (60–91)
T stage, n (%)		
T1a/b	14 (17)	4 (12)
T1c	39 (49)	6 (19)
T2a	23 (29)	12 (38)
T2b	4 (5)	6 (19)
T3	0	4 (12)
Gleason Score		
<6	73 (91)	23 (72)
7	7 (9)	9 (28)
Initial PSA, ng/mL		
<4	17 (21)	3 (9)
4–10	42 (52)	3 (9)
>10–20	20 (25)	16 (50)
>20	1 (1)	10 (31)

TABLE 1
The patients' characteristics

Since 1993, the Royal Marsden Urology Unit has offered an AS policy as a management option for favourable-risk early prostate cancer, and here we describe the preliminary outcome of this approach. The outcome of men managed by WW during the same period was included to illustrate the contrasts between these approaches.

PATIENTS AND METHODS

At the Royal Marsden Hospital, 80 men with early prostate cancer began AS between April 1993 and February 2002. Eligibility requirements included fitness for radical treatment (either radical prostatectomy or radical radiotherapy); clinical stage T1–2, N0/X, M0/X disease; an initial PSA level of ≤20 ng/mL and biopsy Gleason score of ≤7. These 80 patients represent ≈10% of those with localized prostate cancer referred to the Royal Marsden Hospital during this period, with most of the remainder having immediate radical treatment. The AS cohort was a subgroup selected on the basis of favourable prognostic characteristics and according to patient preference. Between 1993 and 2003, 32 patients with clinically localized prostate cancer commenced WW at the institution; there were relatively few because most suitable men would be managed by their local urologist rather than be referred to a tertiary cancer centre. Patients with any T stage, N0/X, M0/X and any presenting PSA level were eligible for WW if they had a Gleason score of ≤7 and were deemed unsuitable for radical treatment, typically because of advanced age and comorbidities. All biopsies were centrally reviewed by a specialist genitourinary pathologist. The patients' characteristics are shown in Table 1.

The AS protocol consisted of serial PSA values and a DRE at 3–6-month intervals for the first 2 years, and every 6 months thereafter. Repeat prostate biopsies were not routinely taken and repeat imaging studies were only used if clinically indicated. The decision between continued monitoring or radical treatment was informed by the rate of rise of PSA, and was made according to the judgement of each patient and clinician. WW included serial PSA values and a DRE at 6-monthly intervals. Hormonal treatment, with either bilateral orchidectomy or LHRH analogue, was indicated if there was symptomatic prostate cancer progression.

In the early 1990s, 11 patients were graded as having well or moderately differentiated disease; to enable comparison, well differentiated tumours were grouped as Gleason ≤6 and moderately differentiated as Gleason 7. Staging investigations included a bone scan and either CT or MRI of the pelvis, but were not used routinely for patients with a Gleason score of <7 and PSA < 10 ng/mL.

The PSADT was calculated using a linear regression of log(PSA) vs time, using all pretreatment PSA values, i.e. (log 2)/k, where k is the slope of the regression line. Categorical data were assessed using the chi-square test and Fisher's exact test, where appropriate. Continuous variables were compared using the Mann–Whitney *U*-test. Univariate and multivariate Cox regression analysis was used to test candidate prognostic factors (T stage, Gleason score, initial PSA level, age) for PSADT. As the PSADT is not evaluable for those patients whose PSA did not increase during the period of observation, k was used as the outcome variable.

RESULTS

At the time of analysis (end of February 2003) the AS group had reached a median (range) follow-up of 42 (1–116) months and 64 (80%) of them remained on AS. Of the remainder, 11 (14%) had received or were receiving radical treatment, and five (6%) had died. No patients developed evidence of metastatic disease, none started palliative hormone therapy, and there were no deaths from prostate cancer. The median (95% CI) actuarial freedom from treatment at 5 years from start of AS was 79.2 (63.9–88.6)% (Fig. 1).

Of the seven patients on AS who had completed radical treatment, all remained biochemically controlled with no clinical evidence of recurrent disease, at a median follow-up of 20 (3–39) months from the date of treatment. Of these seven patients, five received radical radiotherapy and two, radical prostatectomy. One of the surgical cases was pT2b pN0 Gleason 3 + 3 adenocarcinoma with negative margins and a tumour volume of 1.3 mL. The second was pT3a pN0 Gleason 3 + 4 with focal extracapsular extension but specimen-confined disease, occupying 10% of the prostate volume, who received postoperative adjuvant radiation to the prostatic bed. Both patients remain biochemically controlled with a PSA level of <0.04 ng/mL, at a follow-up of 38 and 23 months from surgery, respectively.

At the time of analysis, three patients were undergoing radical radiotherapy and one was awaiting radical prostatectomy. The decision to start radical treatment was made after a median of 13 (3–77) months on AS. The reason for starting radical treatment was the rate of rise of PSA in nine, and the patients' preference in the absence of any increase in PSA in two patients.

The median PSADT was 12 years, while 25% of patients had a PSADT of <4.5 years. The distribution of k against time in the AS group is shown in Fig. 2, which provides an indication of the distribution of PSADT.

There was no significant association between PSADT and either Gleason score or age; there were associations with borderline statistical significance between a rapid PSADT and higher T stage ($P = 0.036$) and initial PSA level ($P = 0.039$). The association between PSADT and T stage ($P = 0.042$), but not initial PSA level ($P = 0.11$), remained statistically significant on multivariate analysis (Table 2).

Comparing the WW with the AS group showed that men on WW were significantly older, with a higher presenting PSA level and higher T stage (all $P < 0.001$). Twenty of the 32 (63%) patients on WW remained on WW at a median follow-up of 41 (7–91) months. Of the remainder, eight (25%) were receiving either continuous or intermittent hormonal therapy, and four (13%) had died, one from hormone-resistant metastatic prostate cancer.

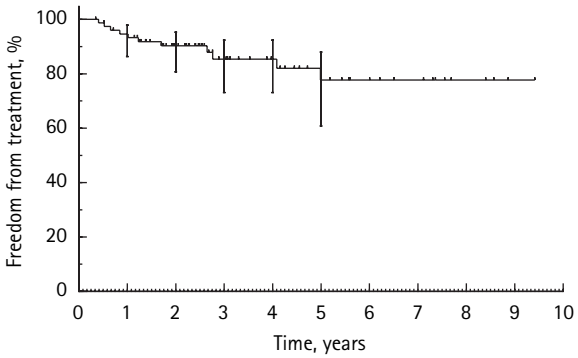

FIG. 1.
Treatment-free survival.

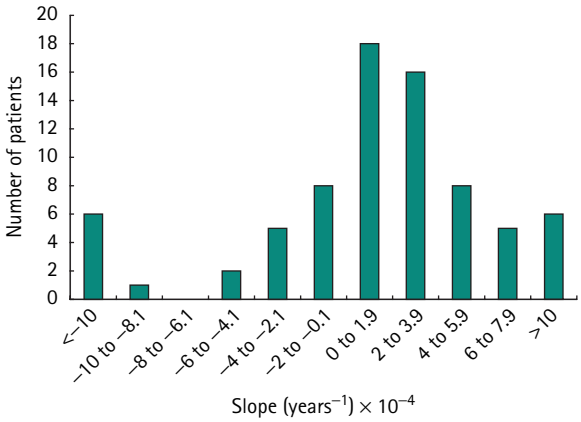

FIG. 2.
The distribution of slope, k((ln2)/PSADT), in the AS cohort.

DISCUSSION

This report shows the feasibility of AS as an approach to managing favourable-risk, early prostate cancer. In this selected series most patients managed by AS avoided the need for treatment of their prostate cancer. The median PSADT of 12 years suggests an indolent course of disease in most patients. Although there was no evidence of clinically progressive disease, long-term follow-up will be required to confirm the safety and efficacy of this approach. The results also illustrate the contrast between WW and AS; whereas WW is a palliative strategy for men who are not expected to live long enough to benefit from radical treatment, AS is a radical strategy for younger men with favourable-risk disease, and which aims to identify the minority for whom curative treatment is necessary.

Although AS has been widely used on an ad hoc basis, the concept was formally described for the first time in 2001 by Choo *et al.* [3] from Toronto, in a report of the preliminary findings from a prospective single-arm study started in 1995. Eligibility was restricted to men with untreated, localized, favourable-grade prostate adenocarcinoma (T1b–T2b N0M0, Gleason score <7 and PSA < 15 ng/mL). Men were followed every 3 months for the first 2 years and then at 6-monthly intervals, with a DRE and PSA testing at each visit. A repeat prostate biopsy was taken at 18 months. Indications for treatment were PSA progression, defined as a PSADT of <2 years, and a final PSA level of >8 ng/mL; histological progression, defined as upgrading to Gleason score ≥8 on re-biopsy; or clinical progression. At the time of the latest update [4], 206 men had entered the study, with a median age of 70 (49–84) years and a median initial PSA level of 6.5 ng/mL. At a median follow-up of 29 months, 137 men (67%) remained on AS within the programme, 48 had received radical treatment, 17 had changed to a WW programme (i.e. no longer appropriate for radical treatment) and four had died from unrelated causes. Of the 48 men who had received 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 (SD) of freedom from disease progression was 67 (12)% at 4 years, suggesting that up to two-thirds of men could be spared radical treatment using this protocol.

Carter *et al.* [5] reported a different surveillance policy in 81 men with a median age of 65 years. Patients had T1c disease, a PSA density of <0.15 and favourable needle biopsy findings (Gleason score ≤6, no Gleason grade 4 or 5 cancer, fewer than three cores involved and less than half of any one core involved). The men were followed with PSA and a DRE at 6-monthly intervals, and an annual prostate biopsy. Radical treatment was recommended for disease progression, defined as unfavourable repeat biopsy findings (any Gleason pattern 4 or 5, more than two biopsy cores involved, or more than half involved in any core). At a median follow-up of 23 months, 25 (31%) had disease progression.

Taken together with the present series, these reports confirm the feasibility of an AS policy,

TABLE 2 The relationship between PSADT and clinical characteristics in the AS cohort

	P	
Variable	Univariate	Multivariate
Gleason grade	0.891	0.521
Age	0.301	0.697
T stage	0.036	0.042
PSA level	0.039	0.110

although the short-term outcome data currently available must be regarded as preliminary. It will be important to assess longer term outcomes, including prostate cancer mortality. However, the long-term prostate cancer mortality associated with WW in men aged 60–70 years with favourable-risk, early prostate cancer is predicted to be ≤10% [6] and it remains uncertain whether immediate radical treatment offers any survival advantage in this setting. While the long-term prostate cancer mortality associated with AS in young, fit men with favourable-risk early prostate cancer is unknown, in the worst possible case it will be as good as that associated with WW in such patients. Avoiding curative treatment in some patients and delaying it by a year or so in others (AS) can be no less effective than avoiding curative treatment in all patients (WW).

These reports highlight the lack of consensus on the criteria used to define disease progression requiring radical treatment in men who are on AS. The current series relied on temporal trends in PSA levels. The John Hopkins criteria are based on the results of repeat biopsies alone [5], whereas the Toronto group have used PSADT, biopsy findings and clinical criteria [3]. At present there is insufficient evidence to determine an optimum AS protocol. The use of the PSADT to guide management is based on the knowledge that preoperative serum PSA levels correlate significantly with the volume of prostate cancer in radical prostatectomy specimens [7], together with the observation that temporal PSA trends in untreated patients conform to an exponential model, suggesting that PSADT is constant over time for a given patient [8]. It seems intuitive that the PSADT will approximate to the rate of tumour growth. In support of this, the PSADT is well established as an important predictor of the risk of metastatic disease [9] and survival [10] in men with PSA failure after radical treatment, and in a report of 113 men on WW, McLaren *et al.* [11] found the PSADT to be the strongest predictor of clinical progression.

If the PSADT is a potentially useful measure of the rate of cancer progression, what is the appropriate threshold to use as an indication for radical treatment? Again it is not possible to make an evidence-based recommendation. The choice of PSADT threshold is necessarily somewhat arbitrary. A more rapid PSADT threshold would spare more men the side-effects of radical treatment, but if too short might merely identify a subset of men with subclinical metastatic disease. However, a longer threshold would mean that fewer men are spared treatment side-effects. The Royal Marsden policy is to use an individualized threshold for each patient, depending on absolute PSA level and life-expectancy (from actuarial tables), and assumes that low-grade prostate cancer seldom becomes symptomatic before the serum PSA level reaches 50 ng/mL. For example, a man with a PSA level of 6 ng/mL needs three PSA doublings before his PSA reaches 50 ng/mL. If his life-expectancy is 10 years, then his PSADT threshold will be ≈3 years. However, if his life-expectancy were 20 years, then a threshold of 7 years would be more appropriate. In practice, the choice of PSADT threshold is an exercise in shared decision-making and is influenced by the relative importance that the patient places on treatment side-effects against possible improvements in longevity.

Initial analyses showed that the variation in the findings between initial and repeat biopsies, at least within the first few years of surveillance, reflect the limitations of sampling rather than tumour development [12]. If high-grade cancer is accepted as an indication for radical treatment, then there is an argument for a more extensive initial biopsy procedure, e.g. 12 needle cores, to minimize sampling error. If initial sampling error can be reduced in this way, subsequent repeat biopsies could then be taken less often.

A prospective study is now ongoing at the Royal Marsden, which aims to optimize the AS protocol, and to serve as a vehicle for translational research. Given the possibility, raised by the current analysis, of an association between PSADT and T stage and initial PSA levels, eligibility is now restricted to men with favourable-risk early prostate cancer (T1 or T2a, Gleason score ≤ 7, PSA <15 ng/mL, less than half of cores positive). Patients are monitored using monthly PSA levels to determine the optimum frequency of PSA testing and the minimum number of observations needed to make an accurate estimate of long-term PSADT. This is an important issue, as the aim of AS is to identify as soon as possible those men who will require treatment, at such a time when that treatment will be curative. Repeat prostate biopsies are taken every 2 years, to identify evidence of histological progression. As part of this study, blood and prostate tissue are being banked for a range of laboratory studies aiming to identify biomarkers of prostate cancer behaviour.

In conclusion, AS is a feasible approach to managing favourable-risk, early prostate cancer. Most men on AS will avoid the need for treatment of their prostate cancer. Ongoing studies are seeking to identify the optimum schedule of PSA testing and repeat biopsy, the appropriate indications for intervention and the long-term efficacy of AS compared with immediate radical treatment.

ACKNOWLEDGEMENTS

This work was undertaken in The Royal Marsden NHS Trust, who received a proportion of its funding from the NHS Executive; the views expressed in this publication are those of the authors and not necessarily those of the NHS Executive. This work was supported by the Institute of Cancer Research, the Bob Champion Cancer Trust, the Cancer Research UK Section of Radiotherapy [CUK] grant number C46/A2131 and NCRI South of England Prostate Cancer Collaborative.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Yao SL, Lu-Yao G.** Understanding and appreciating overdiagnosis in the PSA era. *J Natl Cancer Inst* 2002; **94**: 958–60
2 **Parker CC.** Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol* 2004; **5**: 101–6
3 **Choo R, DeBoer G, Klotz L *et al.*** PSA doubling time of prostate carcinoma managed with watchful observation alone. *Int J Radiat Oncol Biol Phys* 2001; **50**: 615–20
4 **Choo R, Klotz L, Danjoux C *et al.*** Feasibility study. watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. *J Urol* 2002; **167**: 1664–9

5 **Carter HB, Walsh PC, Landis P *et al.*** Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. *J Urol* 2002; **167**: 1231–4
6 **Nicholson PW, Harland SJ.** Survival prospects after screen-detection of prostate cancer. *BJU Int* 2002; **90**: 686–93
7 **Stamey TA, Kabalin JN, McNeal JE *et al.*** Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. *J Urol* 1989; **141**: 1076–83
8 **Schmid HP, McNeal JE, Stamey TA.** Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. *Cancer* 1993; **71**: 2031–40
9 **Parker CC, Dearnaley DP.** The management of PSA failure after radical radiotherapy for localized prostate cancer. *Radiother Oncol* 1998; **49**: 103–10
10 **Sandler HM, Dunn RL, McLaughlin PW *et al.*** Overall survival after prostate-specific-antigen-detected recurrence following conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 2000; **48**: 629–33
11 **McLaren DB, McKenzie M, Duncan G *et al.*** Watchful waiting or watchful progression? Prostate specific antigen doubling times and clinical behavior in patients with early untreated prostate carcinoma. *Cancer* 1998; **82**: 342–8
12 **Epstein JI, Walsh PC, Carter HB.** Dedifferentiation of prostate cancer grade with time in men followed expectantly for stage T1c disease. *J Urol* 2001; **166**: 1688–91

Correspondence: Chris C. Parker, The Academic Unit of Radiotherapy & Oncology, The Royal Marsden NHS Trust and The Institute of Cancer Research, Downs Road, Sutton, Surrey SM2 5PT, UK.
e-mail: chris.parker@icr.ac.uk

Abbreviations: **AS**, active surveillance; **WW**, watchful waiting; **PSADT**, PSA doubling time.