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Prostate Cancer

Medium-term Outcomes of Active Surveillance for Localised Prostate Cancer

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Abstract

Background: Active surveillance (AS) aims to allow men with favourable-risk, localised prostate cancer to avoid unnecessary treatment.
Objective: To describe the clinical outcomes of a prospective study of AS.
Design, setting, and participants: A single-centre, prospective cohort study. Eligibility criteria included histologically proven prostate adenocarcinoma, age 50–80 yr, stage T1/T2, prostate-specific antigen level (PSA) <15 ng/ml, Gleason score (GS) ≤3 + 3 (GS ≤3 + 4 if aged >65 yr), and percent positive biopsy cores (PPC) ≤50%.
Intervention: Patients were assessed by serum PSA level, and digital rectal examination at 3-mo intervals in year 1, 4-mo intervals in year 2, and at 6-mo intervals thereafter. Transrectal ultrasound-guided prostate biopsy was performed after 18–24 mo and every 2 yr thereafter. Treatment was recommended for PSA velocity (PSAV) >1 ng/ml per year or adverse histology, defined as GS ≥4 + 3 or PPC >50%.
Outcome measurements and statistical analysis: Outcomes described, using Kaplan-Meier methods, were rate of adverse histology on repeat biopsy, freedom from treatment, biochemical control after deferred treatment, and overall survival. Analyses using Cox regression were performed to determine predictors of deferred treatment and adverse histology.
Results and limitations: The study enrolled 471 eligible patients from 2002 to 2011. Median age was 66 yr and median initial PSA value was 6.4 ng/ml. Eighty-eight percent of patients had T1 disease and 93% had GS ≤3 + 3. At median follow-up of 5.7 yr, the 5-yr rate of adverse histology and treatment-free probability was 22% (95% confidence interval [CI], 16–29%) and 70% (95% CI, 65–75%), respectively. There were two deaths from prostate cancer. Predictors of time to adverse histology were GS 7, PSAV >1 ng/ml per year, low ratio of free PSA to total PSA, and PPC >25%. Longer follow-up is needed to confirm the safety of this strategy.
Conclusions: This study demonstrates satisfactory medium-term outcomes for AS in selected men with localised prostate cancer.

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1. Introduction

The challenge of localised prostate cancer (PCa) is to distinguish patients with significant cancers who will benefit from radical treatment, from the remainder who will not need any intervention in their lifetime. Active surveillance (AS) is a strategy of close observation with delayed curative treatment in the event of disease

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progression. It aims to avoid the unnecessary treatment of men with harmless PCa, but with timely radical treatment for those who need it. AS has become a standard approach. Data from the British Association of Urological Surgeons database indicate that as many as 40% of UK men with low-risk PCa elect AS [1].

There are no completed, randomised clinical trials comparing AS versus immediate treatment. There are, however, several prospective cohort studies that have reported short- and medium-term outcomes [2–10]. These studies have demonstrated the feasibility of AS and have indicated that most men on AS will avoid the need for radical treatment. However, there are limited data available on longer-term outcomes. This is an important limitation, because it is only with long-term follow-up that we will be able to assess the safety of an AS policy.

We previously reported the early outcomes of a prospective cohort study of AS at the Royal Marsden National Health Service Foundation Trust [11]. We now present updated data from this study.

2. Patients and methods

Eligibility was restricted to men aged 50–80 yr, with histologically proven prostate adenocarcinoma, clinical stage T1/T2, prostate-specific antigen (PSA) level <15 ng/ml, Gleason score (GS) ≤3 + 3 (GS 3 + 4 was permitted in patients aged >65 yr), and percentage of positive cores (PPC) ≤50% of the total number of biopsy cores. Extent of single-core involvement was not an eligibility criterion. Patients were diagnosed in a number of centres with a range of different biopsy techniques, reflecting standard UK clinical practice. Biopsies performed at external institutions were reviewed centrally by a specialist uropathologist. Baseline staging investigations (bone scan and magnetic resonance imaging [MRI] of the pelvis) were not mandatory. Patients were required to be fit for radical treatment based on clinician judgement. Those who were not were followed on a *watch and wait* policy and are not included in this report. All patients gave informed consent and the local ethics committee approved the study.

The AS protocol consisted of clinical assessment with digital rectal examination and serum PSA levels taken at 3-mo intervals in the first year, 4-mo intervals in the second year, and at 6-mo intervals thereafter. The Abbott Architect assay (Abbott Laboratories, Abbott Park, IL, USA) was used. Transrectal ultrasound-guided prostate biopsy was performed after 18–24 mo on surveillance, and every 2 yr thereafter. Radical treatment was recommended in the event of either a PSA velocity (PSAV) >1 ng/ml per year or adverse histology on repeat biopsy, defined as primary GS ≥4 + 3 or the presence of cancer in >50% of the total number of cores. Treatment modality (androgen deprivation therapy [ADT] with radical external beam radiotherapy [EBRT], radical prostatectomy [RP], or brachytherapy) was selected according to local protocol, clinician judgement, and patient preference.

Biochemical failure after deferred radical treatment was defined as a PSA level >0.2 ng/ml after RP, or by the Phoenix criteria (nadir +2 ng/ml) after EBRT [12].

The primary objective of this study was to describe the clinical outcomes of AS. Outcomes analysed were time to adverse histology on repeat biopsy, time to deferred radical treatment, time to biochemical failure after deferred radical treatment, and overall survival. The following variables were assessed for their prognostic impact on time to treatment and time to adverse histology: initial PSA (nanograms per millilitre), GS, T stage, PSAV >1.0 ng/ml per year, ratio of free PSA to total PSA (%fPSA), maximum percentage cancer involvement of any single core, percentage of total biopsy cores containing cancer, number of positive cores, and prostate volume (millilitre).

2.1. Statistical methods

The intention-to-treat population consisted of all patients who consented to the study and who fulfilled the eligibility criteria. The repeat biopsy population included patients who had at least one repeat biopsy after consent. The treated population included all patients who consented to the study, fulfilled the eligibility criteria, and had since started EBRT or had undergone brachytherapy or RP. PSAV was calculated using linear regression based on a minimum of four values and observed over a minimum of 6 mo.

Kaplan-Meier methods were used to describe clinical outcomes. Time was measured from date of diagnosis, and patients were censored at date of last follow-up or death. Time to biochemical failure was assessed in the radically treated population only and was measured from the start date of treatment, which was taken to be the first day of EBRT or date of RP. Patients with no recorded PSA value after treatment were censored at the start of treatment.

Predictors of time to treatment and time to adverse histology were also analysed. Initial univariate analysis was performed using Cox regression to calculate hazard ratios (HR) with 95% confidence intervals (CIs). Variables with p values <0.05 were then included in a multivariate Cox regression model using forward, stepwise methods to include only independently significant variables.

3. Results

Between March 2002 and May 2011, 499 patients with localised PCa were enrolled; 28 patients were ineligible, leaving 471 for analysis. Reasons for ineligibility are listed in Figure 1. The characteristics of eligible patients at consent are shown in Table 1. Median age was 66 yr and median initial PSA value was 6.4 ng/ml. Eight men on surveillance were lost to follow-up.

Table 1 – Patient characteristics

Characteristics	Median (range)*
Age, yr	66 (51–79)
Initial PSA value, ng/ml	6.4 (0.2–14.5)
Risk category, no.	
Low	383
Intermediate	88
%fPSA	18 (0.1–65)
Total biopsy cores, no.	8 (4–18)
Maximum cancer in any single biopsy core, %	10 (1–95)
PPC	16.7% (3.1–50)
PSA velocity, ng/ml per year	0.6 (-6.3–8.1)
Prostate volume, ml	45 (10–159)
PSA density, ng/ml per ml	0.13 (0.04–0.4)
Gleason score, no.	
≤3 + 3	438
3 + 4	33
T stage, no.	
T1	417
T2a	49
T2b	5

PSA = prostate-specific antigen; %fPSA = percentage of free PSA to total PSA.
* Unless otherwise indicated.