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Platinum Priority – Review – Prostate Cancer

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Systematic Review and Meta-analysis of Factors Determining Change to Radical Treatment in Active Surveillance for Localized Prostate Cancer

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Abstract

Context: Many men with clinically localized prostate cancer are being monitored as part of active surveillance (AS) programs, but little is known about reasons for receiving radical treatment.
Objectives: A systematic review of the evidence about AS was undertaken, with a meta-analysis to identify predictors of radical treatment.
Evidence acquisition: A comprehensive search of the Embase, MEDLINE and Web of Knowledge databases to March 2014 was performed. Studies reporting on men with localized prostate cancer followed by AS or monitoring were included. AS was defined where objective eligibility criteria, management strategies, and triggers for clinical review or radical treatment were reported.
Evidence synthesis: The 26 AS cohorts included 7627 men, with a median follow-up of 3.5 yr (range of medians 1.5–7.5 yr). The cohorts had a wide range of inclusion criteria, monitoring protocols, and triggers for radical treatment. There were eight prostate cancer deaths and five cases of metastases in 24 981 person-years of follow-up. Each year, 8.8% of men (95% confidence interval 6.7–11.0%) received radical treatment, most commonly because of biopsy findings, prostate-specific antigen triggers, or patient choice driven by anxiety. Studies in which most men changed treatment were those including only low-risk Gleason score 6 disease and scheduled rebiopsies.
Conclusions: The wide variety of AS protocols and lack of robust evidence make firm conclusions difficult. Currently, patients and clinicians have to make judgments about the balance of risks and benefits in AS protocols. The publication of robust evidence from randomized trials and longer-term follow-up of cohorts is urgently required.
Patient summary: We reviewed 26 studies of men on active surveillance for prostate cancer. There was evidence that studies including men with the lowest risk disease and scheduled rebiopsy had higher rates of radical treatment.

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1. Introduction

Active surveillance (AS) is increasingly used as an alternative to immediate radical intervention for men with clinically localized prostate cancer who are at low risk of progressing to life-threatening disease [1]. Radical treatment comes with a fairly high risk of harm [2], so there is strong motivation to radically intervene only in cases with high risk of progression. AS involves regular follow-up with prostate-specific antigen (PSA) testing, digital rectal examination (DRE), review of symptoms, and/or repeat biopsy. Surveillance also requires predefined triggers for clinical review so that radical treatment can be initiated where possible for those with progressing disease. There is no formal evidence on whether AS is a safe management option for men with clinically localized prostate cancer. Two randomized trials have evaluated the effectiveness of a passive strategy called watchful waiting (ie, palliative treatment once symptoms appear). The Prostate Cancer Intervention versus Observation Trial (PIVOT) recently found no difference between watchful waiting and radical prostatectomy for either all-cause or prostate cancer mortality after at least 10 yr of follow-up [3]. The PIVOT cohort was relatively elderly (mean age 67 yr at enrolment) and the majority had screen-detected low-risk disease. The SPCG-4 study [4,5] found that radical prostatectomy reduced prostate-specific mortality compared to watchful waiting after a median of 13.2 yr among men who had been diagnosed clinically.

Previous systematic reviews [6–8] have found little consensus on eligibility criteria, protocols for surveillance, or triggers for recommending radical intervention. These various strategies for AS have led to widely different rates of change to radical treatment between AS studies [6–8]. We undertook a systematic review and meta-analysis to investigate rates of change to radical treatment and the key AS strategy factors influencing change of treatment.

2. Evidence acquisition

2.1. Search strategy

We conducted a systematic search of the MEDLINE, Embase, and Web of Science online databases from October 2004 (the end date of our previous systematic review [6]) to April 2013. A forward citation search of the five studies [1,9–12] included by Martin et al [6] was also performed using the Web of Science database. An update using the same search strategy was carried out by A.J.S. alone in March 2014. Further information about our evidence acquisition and synthesis can be found in the Supplementary material online.

2.2. Inclusion criteria

We included studies involving men with T1–T2 clinically localized prostate cancer that was initially managed conservatively, and in which predefined clinical, pathological, or biochemical criteria for clinical review were outlined. Studies involving recurrence after radical prostatectomy or radiotherapy (ie, not initially managed conservatively) were excluded. We excluded any reviews, editorial comments, background papers, and studies involving different treatments and diseases of the prostate.

2.3. Data extraction and synthesis

Eligibility criteria, surveillance protocols, sample size, age, PSA, follow-up times, treatment change triggers, treatment change rates, metastases, prostate cancer–specific mortality, and reasons for changing treatment were extracted manually from each paper by A.J.S. and checked by one of C.M., K.T., or R.M.M. Authors of publications found in our search were contacted to provide further data where necessary and to check that data extraction was correct.

2.4. Study outcomes

Treatment change rates are considered here as key short-term outcome measures for AS, and the occurrence of metastases and/or prostate cancer death are longer-term outcomes. To account for both sample size and duration of follow-up in the cohorts, person-years were used in calculating the rate of change to radical treatment. Person-years were estimated as the median follow-up time multiplied by the sample size for each study; total person-years were the sum of these across the studies included.

2.5. Meta-analysis methods

A meta-analysis was conducted to estimate the rate of change to radical treatment per person-year. This rate was calculated for each study as

$$\frac{\text{radical treatment events}}{\text{sample size} \times \text{median follow-up time}}.$$

Heterogeneity between studies was measured using the I^2 statistic [13]: a higher I^2 value indicates higher between-study heterogeneity. Meta-regression was performed to examine the associations of study characteristics with rates of change to radical treatment. The study characteristics considered were (1) year of first recruitment; (2) whether the study restricted participation to those with Gleason grade 3 + 3 or less; (3) whether the study limited inclusion to men with PSA $\leq$10 ng/ml; (4) the number of scheduled PSA tests in the first 3 yr; (5) whether the study protocol included scheduled rebiopsy; and (6) whether PSA or PSA kinetic measures, such as PSA doubling time (PSADT) or PSA velocity (PSAv), were used to recommend clinical review or radical treatment. Together with univariate analysis, two multivariable meta-regressions were performed, grouping eligibility variables (1)–(3) and monitoring procedure variables (4)–(6).

Several studies had conducted within-cohort analyses to relate patient characteristics to the change to radical treatment. For cases in which more than two studies reported estimates of the association of a patient characteristic with change to radical treatment, we carried out a meta-analysis of these estimates. We also used meta-analysis to examine the reasons for changing to radical