Continuing Controversy Over Monitoring Men With Localized Prostate Cancer: A Systematic Review of Programs in the Prostate Specific Antigen Era

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Purpose: There is continuing controversy over the most appropriate treatment for screen detected and clinically localized prostate cancer, and increasing interest in monitoring such men initially with radical treatment targeted at cancers showing signs of progressive potential but while they are still curable. Current evidence on monitoring protocols and biomarkers used to predict disease progression was systematically reviewed.

Materials and Methods: The MEDLINE and Excerpta Medica (EMBASE) bibliographic databases were searched from 1988 to October 2004, supplemented by manual searches of reference lists, focusing on studies reporting monitoring of men with localized prostate cancer.

Results: A total of 48 potentially eligible articles were found but only 5 studies, in which there was a total of 451 participants, restricted entry criteria to men with clinically localized (T1-T2) prostate cancer. Monitoring protocols varied with little consensus, although the majority used prostate specific antigen and digital rectal examination, while some added re-biopsy to assess progression. Actuarial probabilities of freedom from disease progression at 4 to 5 years of followup were 67% to 72%. However, up to 50% of men abandoned monitoring within 2 years, largely because of anxiety related to increasing prostate specific antigen rather than objective evidence of disease progression. There was no robust evidence to support prostate specific antigen doubling times or velocity to identify men in whom disease may progress. Studies were characterized by small sample size, short-term followup, observer bias and uncertain validity around variable definitions of progression.

Conclusions: Current evidence suggests that some form of monitoring would be a suitable treatment option in men with localized prostate cancer but there is little consensus over what markers should be used in such a program or how progression should be properly defined. The search for a method that safely identifies men with prostate cancer who could avoid radical intervention must continue.

Key Words: prostate, prostatic neoplasms, prognosis, disease progression, prostate-specific antigen

Annually more than 500,000 men worldwide are diagnosed with prostate cancer, accounting for 10% of all male incident cancers,[1] and it is rapidly becoming the most common cancer in men. Autopsy studies show that cancerous cells can be found in the prostate of 30% to 40% of men at age 60 years, increasing to 60% to 70% by age 80 years, and yet in a 50-year-old man in the United States the lifetime risk of clinical and fatal prostate cancer is estimated to be only 9.5% and 2.9%, respectively.[2] The dilemma is that, although most cancers detected by screening are clinically confined to the prostate and, hence, are potentially curable, current screening tests cannot differentiate between cancers that have low biological likelihood of progression and those with more aggressive potential.[3] Furthermore, there is uncertainty about the effectiveness of radical surgery and radiotherapy for screen detected disease.[4] Thus, screening may result in substantial over diagnosis and over treatment of clinically insignificant prostate cancer.

The doubts surrounding the benefits of screening and early radical treatment have led in recent years to increasing use of monitoring, variously termed active monitoring, surveillance or watchful waiting, as a therapeutic option.[4] This involves regular followup using 1 or more of certain investigations in men with clinically localized cancers, including PSA testing, DRE, review of symptoms and sometimes TRUS guided re-biopsy. These investigations aim to determine which cancers should be treated with potentially curative interventions and when this should be done. This differs from traditional watchful waiting regimens, in which followup typically waited for the development of systemic disease and the therapeutic goal was palliation. Appropriate targeting of active monitoring requires markers that can differentiate between indolent tumors and those with aggressive potential suitable for radical curative treatment.[4] However, the most appropriate frequency and form of followup in patients choosing active monitoring remains undefined.[3] We performed a systematic review of the literature to identify and review studies done in the PSA testing era

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(after 1988) that followed men initially treated conservatively with watchful waiting or active monitoring. We documented the risk of progression and related this to potential markers of disease progression.

METHODS

The MEDLINE and EMBASE bibliographic databases were searched between 1988 and October 2004 using certain combinations of MeSH headings and text word search terms, including exp Prostatic Neoplasms/ or (prostat$ adj5 neoplas$).tw. or (prostat$ adj5 cancer$).tw. AND exp Disease Progression/ or exp Survival Analysis/ or exp Natural History/ or (expectant$ adj5 manage$).tw. or (conservative$ adj5 manage$).tw. or (active adj5 surveillance).tw. or (watchful adj5 waiting).tw. or (watch adj5 wait).tw. or (watchful adj5 observation).tw. or (active$ adj5 monitor$).tw. or (defer$ adj5 treatment).tw. Reference lists of eligible studies and review articles were also searched.

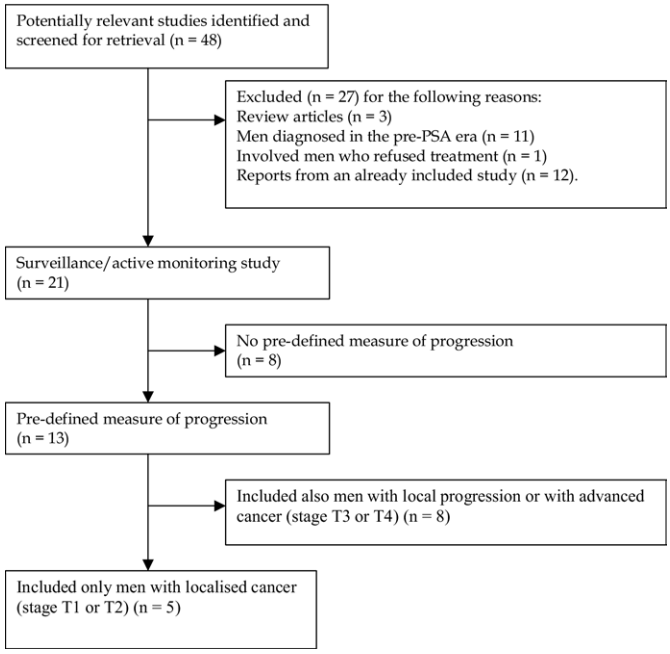
Studies were included if they involved men with localized prostate cancer that was initially managed conservatively and if potential biomarkers of disease activity were related to an objective clinical, pathological or biochemical assessment of whether disease had progressed. Eligibility criteria and followup protocols, progression definitions, triggers for recommending treatment, the relationship between biomarkers and progression, the proportion of men undergoing active treatment and the reasons for treatment were documented.

Reports of active monitoring with curative intent that investigated predictors of subsequent radical treatments in the absence of predefined objective measures of disease progression were included separately with data abstracted on the proportion of men subsequently choosing radical treatment and their reasons for abandoning active monitoring.

RESULTS

The search resulted in a total of 2,946 articles, of which 48 were potentially eligible (see figure). Of these studies 27 were excluded (references available on request). Eight of the 21 remaining studies appeared to offer active monitoring protocols with curative intent but without predefined objective measures of progression (table 1).[5–12] All 8 studies were based on retrospective case note reviews and they were small scale with a median sample size of 186.5 men (range 49 to 1,158) with 6 limited to men with localized (stage T1-T2) disease.[5–10] These reports showed that 22% to 73.2% of men abandoned active monitoring within 2 to 5 years[6–12] with patient preference the most commonly cited factor by physicians.[6,9,10] Higher baseline PSA and tumor stage,[11] and short PSA doubling time (less than 2 to 3 years)[6,7] were associated with higher subsequent rates of active treatment, while older age[8,11] and adverse pretreatment social circumstances[8] were associated with lower rates of choosing active treatment.

The 13 remaining studies had predefined objective measures of progression[13–25] but 8 included men with advanced disease (stage T2-T3) who were followed with palliative intent (tables 2 and 3). The remaining 5 reports were limited to localized (stage T1-T2) prostate cancer[13–16,23] involving a total of 451 men (median 78, range 27 to 206). This review focuses on these 5 studies,[13–16,23] of which 2 are retrospective case note reviews[13,15] and 3 are prospective case series (tables 4 and 5).[14,16,23]



Number of studies included and excluded from review

Eligibility Criteria (tables 4 and 5)

Average age in the men was between 65 and 71.5 years but only 2 studies restricted the upper age to about 75 years to include those potentially eligible for radical treatment.[14,23] The proportion of men with stage T1c was 100% in 2 studies,[14,23] 55% to 60% in 2[13,16] and 0% in 1, including only T1a disease.[15] In 3 studies histological criteria were specified for inclusion[13,14,16] and 1 required PSA density less than 15 ng/ml/cm^3 for a participant to be eligible.[14] In all except 1 study[15] the men were followed an average of less than 5 years.

Definitions of Disease Progression

Active monitoring studies revealed different protocols for monitoring and diagnosing disease progression (tables 6 and 7). All protocols included serial PSA and DRE assessment, while 3 included repeat TRUS guided biopsies[13,14,16] and others included various clinical measures (table 4). Progression rates for T1c-T2 disease were between 17% and 33% with little clear relationship with median duration of followup, mean age or median initial PSA. A large proportion of men underwent radical treatment without clinical evidence of progression, usually because of anxiety or withdrawal prompted by PSA progression. For example, Patel et al reported that only 17 of 31 men changing to radical treatment met the criteria for progression.[13]

In the Johns Hopkins series 13% of men (9 of 70) showed a change in Gleason score of 6 or less to 7 or greater on repeat biopsy.[26] In 8 of these men the change occurred within 15 months of initial sampling. Patel et al found that 23% of men with localized prostate cancer had worse Gleason scores within 6 months of initial biopsy, while 61% had no cancer detected at repeat biopsy.[13] In a case series that included 4% of men with stage T3 a total of 53% (24 of 45)