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Meaningful End Points and Outcomes in Men on Active Surveillance for Early – Stage Prostate Cancer

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Summary

Purpose of Review—Active surveillance is a management strategy for early stage prostate cancer designed to balance early detection of aggressive disease and overtreatment of indolent disease. We evaluate recently reported outcomes and discuss the potentially most important endpoints for such an approach.

Recent findings—The past two years have seen the publication of two trials of watchful waiting versus immediate treatment and updates of multiple active surveillance cohorts for men with early stage prostate cancer. The watchful waiting trials demonstrated a small potential mortality benefit to immediate treatment when applied to all risk levels (6% absolute difference at 15 years), emphasizing the importance of a risk adapted strategy. In reported active surveillance cohorts, prostate cancer death and metastasis remain rare events. Intermediate outcomes such as progression to treatment and upgrading/upstaging on final pathology appear consistent among cohorts but must be interpreted with caution when compared to historical controls of immediate treatment due to potential selection bias.

Summary—The safety of active surveillance has been reinforced by recent reports. Accumulation of additional data on men with intermediate risk cancer and development and validation of new biomarkers of risk will allow refined and, likely, expanded use of this approach.

Keywords

active surveillance; outcomes; prostate cancer

Introduction

The increased detection of localized, low-risk prostate cancer during the PSA era is a well-documented phenomenon. In an effort to reduce overtreatment of indolent disease, active surveillance has emerged as a viable management option for men with low-risk prostate cancer. It is important to differentiate active surveillance, which involves close surveillance of the patient with intention to deliver definitive, local therapy if there are signs of aggressive disease before widespread dissemination, from watchful waiting, which defers

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Conflicts of Interest

none

treatment until dissemination and then provides systemic or palliative therapy. The SPCG-4 and PIVOT trials have shown us that there is a likely benefit to immediate treatment over watchful waiting, but this difference is small when men with low-risk disease and shorter life spans are included.[1,2] The NCCN now recommends active surveillance as a treatment option for patients with very low and low-risk prostate cancer.[3] Multiple institutions have reported their experience with active surveillance. The aim of this article is to review outcomes reported from active surveillance studies and consider the validity of end points other than overall survival (OS) and cancer specific survival (CSS).

Appropriate Outcomes

The goal of active surveillance is to delay or avoid treatment and treatment-related morbidities in men with clinically indolent prostate cancer without exposing men with aggressive cancer to an increased risk of disability or death due to prostate cancer. Ultimate endpoints and surrogate outcomes are used to measure the oncologic results of active surveillance and can be compared to other management strategies. Cancer-specific, and metastasis-free survival are ultimate end points by which active surveillance should be evaluated. However, due to the slow growing nature of low-risk prostate cancer, prospective evaluation of these endpoints requires 10 to 15 years or longer. The use of surrogate outcomes could provide more timely guidance for clinicians and patients. For a surrogate outcome to be valid and effective it should be readily and consistently measurable, strongly correlated with the outcome of interest, and reflect the impact of any given treatment on the outcome of interest.[4] Potential surrogate outcomes in prostate cancer include asymptomatic prostate cancer metastases, biochemical progression after delayed treatment, use of androgen deprivation therapy, and, to a limited extent, adverse pathologic features at the time of treatment. Another set of outcomes is used to describe the experience of men on active surveillance. These outcomes include time to treatment and treatment rates, biopsy and monitoring related complications, and quality of life measures. While these outcomes are important information when advising men on their treatment decision, they should not be used to judge the success or failure of active surveillance.

Survival

Very few deaths due to prostate cancer have been reported from multiple large active surveillance cohorts. Godtman, *et al.* reported one death due to prostate cancer among 439 men in the Göteborg cohort with a median follow-up of 6 years. The death occurred in a patient with intermediate-risk disease who deferred initial treatment prior to receiving hormonal therapy. He died 12.6 years after diagnosis.[5] Klotz reported 5 deaths due to prostate cancer among 450 patients managed with active surveillance at the University of Toronto at a median follow-up of 6.8 years. Of the five, one was intermediate risk at the time of enrollment based on a Gleason score of 7. All 5 of these patients were reclassified into a higher risk disease category based on a PSA doubling time of less than two years and were offered treatment. Three of these patients elected local treatment of their prostate cancer while two refused. Four of the five patients progressed in the first two years while on study.[6] Selvaduri *et al* noted two deaths in a recently reported series of 471 patients from the

Royal Marsden Hospital followed on active surveillance median of 5.7 years. Both of these patient progressed on the first confirmatory biopsy while on active surveillance.[7]

Several other large cohorts have reported results from a combined 3,990 patients with no deaths seen and median follow-up ranging from 1.6 to 4.3 years.[8]. The largest of these studies, the Prostate Cancer Research International: Active Surveillance (PRIAS) study, included 2494 patients but follow-up was short (median 1.6 years.)[9] At UCSF, our recently updated results of 465 men followed for a median of 4.3 years following diagnosis (range 0.7 to 14.8 years), including 56 men with intermediate risk disease by the Cancer of Prostate Risk Assessment (CAPRA) criteria, also showed no deaths and no metastases.[10]

In summary, multiple large active surveillance cohorts with short to intermediate term follow-up have shown that prostate cancer death following management with active surveillance is a rare event. With time, we will likely see additional prostate cancer related events reported. What is not clear is how many of these deaths could be prevented with immediate intervention. A recent study of men with low-risk prostate cancer undergoing active surveillance and men who received radical prostatectomy predicted that prostate cancer specific death would be slightly more common among those managed with active surveillance as compared to radical prostatectomy (3.4 versus 2.0%, respectively).[11] As the authors note, this small difference may be offset by gains in quality of life from those who delay or avoid treatment. Unfortunately, this could not assessed in their model due to insufficient data on changes in quality of life on active surveillance.

Intermediate Outcomes

The low mortality and metastasis rates and still relatively short follow-up in active surveillance cohorts when compared to the natural history of low risk prostate cancer[12] require consideration of surrogate outcome measures when evaluating active surveillance.

Post-Treatment Outcomes

Several studies have examined the oncologic outcomes of men who delay initial treatment for prostate cancer, although many of these studies have not been in men managed with active surveillance. One recent study examined the effect of treatment delay on 1561 men with low and intermediate risk prostate cancer in the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Among patients with low-risk disease, there was no difference in adverse pathology at the time of surgery or biochemical recurrence following surgery for those who had delayed surgery. However, those with intermediate-risk disease who delayed surgery more than 9 months had a higher risk of positive surgical margins and higher risk of biochemical recurrence.[13] While these results suggest that men diagnosed with intermediate risk disease may suffer disease progression and worse oncologic outcomes if surgery is delayed, the relation to active surveillance is not clear since the patients in this study were not followed by an active surveillance protocol and there was likely selection bias in those who underwent treatment. We previously reported that men with low-risk disease undergoing radical prostatectomy after a period of surveillance experienced no increase in adverse pathologic outcomes.[14] However, when men with intermediate risk

disease were included, there was a higher rate of non-organ confined disease (27% v. 19%) and positive surgical margins (15% v. 9%) in the active surveillance plus surgery versus the immediate surgery group. Neither difference was statistically significant.[15] While worth noting, the use of adverse pathology at the time of treatment as an outcome is limited since this can only be assessed among men treated with surgery. It is unclear if those with adverse pathologic features suffer a worse oncologic outcome following active surveillance since no patient in the active surveillance plus surgery group had experience biochemical recurrence at the time of last follow-up. Finally, the goal of active surveillance is to select those with more aggressive disease for treatment while sparing those with indolent disease. If this goal were achieved, one would expect higher rates of aggressive pathologic features in the patients who progressed to surgery on active surveillance when compared to all men with low-risk disease since men with more indolent disease will never progress to surgery on active surveillance. This selection bias highlights the caution one must use when evaluating intermediate end-points for active surveillance, especially when they are compared to historical controls.

Disease Progression and Treatment Free Survival

There is no standard definition of disease progression necessitating treatment while on active surveillance. Again, progression (and subsequent treatment) is to be expected in some men and is a natural consequence of active surveillance. Potential progression criteria include PSA kinetics, increased volume and/or grade of cancer on biopsy, or progression based on DRE or imaging.

One commonly used parameter is a change or increase in volume or grade of prostate cancer on repeat biopsy. With each repeat biopsy, approximately 10% of patients will have an increase in tumor volume and 20–30% will have in increase in tumor grade.[16,17] The recent report of the UCSF experience noted that 220 of the 465 men (47%) progressed on multiple repeat biopsies. Of these, 44 progressed by volume alone (20%) and 176 progressed by grade alone or grade and volume (80%). Higher PSA density and a positive confirmatory biopsy were the strongest predictors of pathologic progression.[10] Several other studies have reported rates histologic upgrading of 12% to 30.6% depending on the criteria for inclusion and the definition of upgrading.[7–9,18,19]. Biopsy progression has been the most common reason for treatment in multiple cohorts.[20] There are, however, several issues with using biopsy progression as an absolute indication for treatment. First, it is well established that approximately 30% of men who undergo prostatectomy for low-risk disease will have a higher Gleason score on final pathology. Therefore, ‘early progression’ in many men on active surveillance likely reflects more accurate sampling of an initially under-staged tumor.[21] Second, since the inclusion criteria for active surveillance are an arbitrary set of parameters that define low-risk disease, defining progression as the point when the sampled disease has progressed beyond the inclusion criteria is arbitrary as well and may still result in overtreatment. This problem is magnified when one considers that grade progression in some cases due to a very small part of tumor being called pattern 4 and this may not be reproducible among pathologists.[22] When these factors are considered together, it is likely that many of the 30–40% of men who experience biopsy-based disease progression have not actually had true disease progression.

The value of PSA kinetics in recommending treatment has been questioned. In the University of Toronto experience, PSA doubling time of less than 2 years has been used to trigger therapy. In a recent report of this cohort, 48% of men treated and 14% of the entire cohort were treated for PSA kinetics alone.[6] An increase in PSA of > 1ng/ml per year was also used as an independent trigger for local therapy at the Royal Marsden Hospital.[7] At UCSF, we have found that a PSA density of > 0.15 at enrollment is one of the few independent predictors of the likelihood of biopsy progression (OR 2.35, 95% CI 1.31–4.22 at 3 years).[10] However, several papers have shown that when PSA kinetics, at least over the short- to intermediate-term, do not independently predict unfavorable pathology or outcome at the time of treatment.[23–25] We, and others, do not routinely use PSA as an independent recommendation for treatment.[6]

Rates of treatment have been consistent across multiple cohorts, most commonly ranging from 30–40%.[6–8,15] Not surprisingly, the likelihood of remaining on active surveillance and treatment free decreases over time and was 45.4% at 10 years in the Göteborg trial.[5] Over time, more data on long-term adherence and treatment free survival will become available. In the future, expansion of the active surveillance criteria may affect treatment rates, although at the same time improved imaging and disease risk stratification may allow us to spare more patients treatment for longer. In addition, more long-term data and improved strategies for dealing with patient anxiety while on active surveillance should decrease the number of patients treated in the absence of progression.

Regardless of the criteria used to define disease progression and advise treatment, this outcome should not be viewed in a negative light. Rather, the time to treatment and ability to remain treatment free is an important measure of the benefit of active surveillance.

Quality of Life

Maintaining the overall quality of life of men with prostate cancer is one of the key goals of active surveillance. While the benefit of avoiding the side effects of surgery and radiation early are clear, the effects mental health and overall quality life are less so. Several prior studies of watchful waiting versus intervention, including a retrospective review from the CaPSURE database, have shown that while those on watchful waiting avoid early declines in physical quality of life, they experienced greater declines in mental health related to anxiety and depression which affects their overall health-related quality of life (HQROL). In addition, the majority of men on watchful waiting had decreases in sexual function over time.[26] However, patients who have historically elected watchful waiting are a different group of patients than those on active surveillance with a higher overall burden of medical illness, which would be expected to decrease overall HRQOL. Results for SPGC-4, the randomized Scandinavian trial comparing radical prostatectomy to watchful waiting showed similar level of high HQROL 12 years following diagnosis.[27] Several studies have shown excellent HRQOL in the first year after enrollment in active surveillance including recent results from the Finnish and Italian arms of the PRIAS study.[28,29] Given the results of prior studies of quality of life for watchful waiting versus intervention, longer-term follow-up of quality of life on active surveillance with validated questionnaires is needed.[30]

Conclusions

As active surveillance gains in popularity worldwide, ongoing assessment of patient outcomes will affect its use. While there are still no reported results of trials randomizing men to immediate intervention, the ProtecT trial in which men were randomized to active surveillance, radical prostatectomy, and radiation therapy, is scheduled to close soon. This will further our knowledge of outcomes on active surveillance and allow better understanding of the results seen from observational cohorts to this point. In the future, further assessment of outcomes for men with intermediate risk disease will be important as will tools that better help predict a man's risk of clinically significant disease. There has been much recent attention to the role of imaging and biomarkers in monitoring men while on active surveillance.[31] Tissue-based and circulating biomarkers may improve our ability to predict one's likelihood of progression or harboring more aggressive disease. The Canary Prostate Active Surveillance Study is one large, multi-institutional cohort that established a tissue bank for the evaluation of these potential markers and has been used to evaluate the utility TMPRSS2:ERG fusion and PCA3 as prognostic factors in men on active surveillance.[32,33] Several other biopsy-based gene assays have been recently FDA approved for men with newly diagnosed prostate cancer.[34,35] The utility of these markers in increasing (or decreasing) the number of men who are good canidates for surveillance requires better validation. The use of intermediate endpoints and surrogate markers that accurately reflect an individuals long-term risk of morbidity and mortality will be critical to maximizing the utility of active surveillance.

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Key Points

- Overall Survival, prostate cancer specific survival, and metastasis free survival are the ultimate outcomes by which active surveillance should be evaluated.
- The long natural history of early-stage prostate cancer requires consideration of intermediate outcomes.
- Intermediate outcomes such as pathologic disease progression and PSA kinetics must be interpreted with caution due potential selection bias.
- Accumulating data on the outcomes of men with intermediate risk prostate cancer managed with active surveillance may allow expansion of active surveillance inclusion criteria.
- Further validation of biochemical markers and advanced imaging techniques may provide better surrogates for clinically significant disease in the future.