Active surveillance for good risk prostate cancer: rationale, method, and results

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KLOTZ LH. Active surveillance for good risk prostate cancer: rationale, method, and results. The Canadian Journal of Urology. 2005;12 (Supplement 2):21-24.

Background: *Many newly diagnosed patients with prostate cancer have "good risk" disease. The challenge is to identify the minority of these patients with aggressive disease and offer them curative treatment, while sparing the remainder the morbidity of unnecessary treatment.*

Purpose: *To examine the results of active surveillance with selective delayed intervention in good risk prostate cancer patients.*

Materials and methods: *This was a prospective phase II study of active surveillance of 299 patients. Eighty percent (239 patients) met the criteria for good risk disease: PSA < 10 ng/mL, Gleason ≤ 6, T ≤ 2a. Twenty percent of patients, all of whom who were age 70 or greater, had Gleason 7 cancer or a PSA above 10.*

Results: *At 8 years, overall survival is 85% and disease-specific survival is 99%. A PSA doubling time of < 2 years was linked with likelihood of locally advanced disease.*

Conclusion: *Watchful waiting is clearly appropriate for elderly prostate cancer patients with high co-morbidities. For good risk, young, healthy patients, this study supports the feasibility of long-term, close monitoring with early intervention for those who progress rapidly. Approximately two thirds of such patients will remain free of treatment over 8 years.*

Key Words: prostate cancer, surveillance, watchful waiting, good risk

Introduction

A strategy of prostate cancer screening based on prostate biopsy for patients with elevated levels of PSA or abnormal DRE results in diagnosing many patients whose disease does not pose a threat to their life. The prevalence of histological prostate cancer in men over 50 years old is 30%-40%.[1-4] A large proportion of this histological, or 'latent' prostate cancer is never destined to progress or affect the lifespan of the patient. The lifetime risk of being diagnosed with prostate cancer has almost doubled, from 9.5% in the pre-PSA era to 17.1% currently.[5-7] In a recent prostate cancer prevention study, a strategy of routine systematic biopsies of the prostate in all men, regardless of PSA, resulted in 24.4% of patients in the placebo arm diagnosed with prostate cancer over a seven year period.[8] Meanwhile, the risk of dying from prostate cancer remains at approximately 3%.[7] As the lifetime risk of being diagnosed approaches the known rate of histological (mostly insignificant) prostate cancer, the risk of overtreatment looms large. At least two studies have tried to model the overdiagnosis rate, suggesting it is from 30% to 84%.[9,10] Factors contributing to this are the increasing use of PSA screening and more extensive biopsy strategies employing 8 to 13 cores.[11] Additionally, biopsies are often repeated until a cancer diagnosis is made.[12] The majority of newly diagnosed patients now have good risk, T1c prostate cancer. The central challenge in these patients is to identify the minority of patients with aggressive prostate cancer, and offer them curative treatment, while sparing the remainder the morbidity of unnecessary treatment.

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Active surveillance studies

Since the prediction of clinically insignificant disease is problematic and inaccurate, an alternative strategy

TABLE 1. **Criteria for progression on active surveillance as per Choo et al[16]**

PSA progression (all 3 of)
- PSA doubling time < 2 years, based on at least 3 separate measurements over a minimum of 6 months (authors have increased threshold to PSA DT < 3 years in 2003)
- Final PSA > 8 ng/ml
- P value < 0.05 from a regression analysis of ln (PSA) on time

Clinical progression (any one of)
- More than twice increase in the product of the maximum perpendicular diameters of the primary lesio as measured digitally
- Local progression of prostate cancer requiring TURP
- Development of ureteric obstruction
- Radiological and/or clinical evidence of distant metastasis

Histologic progression
Gleason score ≥ 8 on rebiopsy of prostate at 12-18 months

has been developed that allows patient entry into an expectant management protocol with rigorous monitoring and the option of salvage curative therapy should signs of progression develop. This is referred to as active surveillance.[13,14]

Choo and Klotz were the first to report on a prospective active surveillance protocol incorporating selective.[15,16] Eligibility criteria are summarized in Table 1.

The current cohort comprises 299 patients. Eighty percent of the patients in this series fulfilled the criteria for favorable disease (PSA < 10 ng/ml, Gleason ≤ 6, T ≤ 2a). The median age was 70 with a range of 49 to 84. Eighty percent of patients had Gleason 6 or less, and the same proportion had a PSA < 10 ng/mL (median = 6.5 ng/mL). With a median follow up of 64 months, 101 patients (34%) came off watchful observation while 198 have remained on surveillance. Fifteen percent of patients came off surveillance because of rapid biochemical progression; 3% for clinical progression; 4% for histologic progression; and 12% due to patient preference. At 8 years, overall survival is 85% at 8 years; disease specific survival is 99% Only 2/299 patients have died of prostate cancer. Both patients had a PSA DT < 2 years. Both deaths occurred 5 years after diagnosis. This suggests that both of these patients had occult metastases at the time of diagnosis, and their outcome would not have been altered by earlier treatment.

The distribution of PSA doubling times (PSAdt) is seen in Figure 1. The median PSAdt was 7.0 years. Twenty two percent of patients had a PSA doubling time < 3 years. Forty two percent had a PSAdt > 10 years, suggesting an indolent course of disease in these patients.

Patients were re-biopsied 1.5-2 years after being placed on the surveillance protocol. Grade remained stable in 92%; 8% demonstrated significant (≥ 2 Gleason score) rise. Whether this represents true grade progression or initial undersampling is unknown. Regardless, it is consistent with other similar series, demonstrating a 12.9% rate of grade progression over 2-3 years.[17]

Twenty-four of the patients in this cohort have had a radical prostatectomy for a PSA doubling time < 2 years. All had Gleason 5-6, PSA < 10, pT1-2 at study entry. Final pathology was as follows: 10 (42%) were pT2; 14 (58%) were pT3a-c; 2 (8%) were N1. For a group

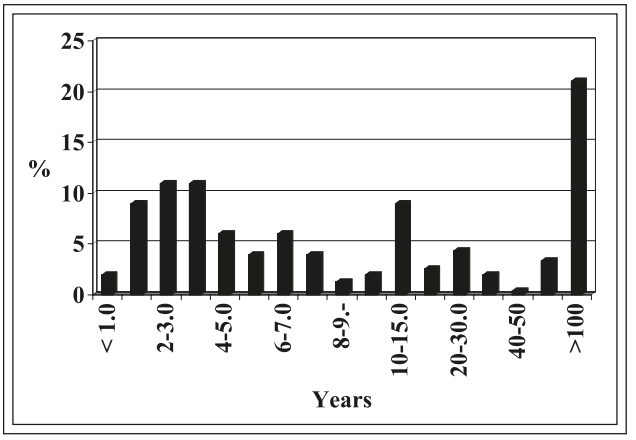

Figure 1. Doubling times of PSA in 299 patients on an active surveillance protocol. The data is based on a median follow up of 55 months. Median PSA doubling time was 7.00 years.
Median number of measurements was 7 (range 3-19). Twenty-two percent of patients had a PSAdt < 3 years.

TABLE 2. **Predicting insignificant prostate cancer based on PSA and biopsy core information. For all studies, the gold standard was < 0.5 cc of Gleason ≤ 3 pattern cancer in the radical prostatectomy specimen.**

Author	PSA density	# Cores positive	Max % of core pos.	Grade	% tissue positive	Extent (mm)
Epstein[18]	< 0.10	< 3	< 50%	≤ 6		
Irwin[28]		1		≤ 6		< 3 mm
Cupp[27]		1		≤ 6		< 3 mm
Goto[21]	< 0.10	1		≤ 6		< 2 mm
Epstein[19]	F/T > .15	< 3	< 50%	≤ 6		
Noguchi[24]	< 0.15	1		≤ 6		< 3 mm
Augustin[23]	< 0.10				≤ 1%	
Anast[29]			< 10%	≤ 6		

of patients with favorable clinical characteristics, this is a high rate of locally advanced disease.

This supports the view that a short PSAdt is associated with a more aggressive phenotype. A PSAdt < 2 years, in patients with otherwise favorable clinical features, portents a high likelihood of locally advanced disease. This also suggests that, insofar as cure of the patients with early rapid biochemical progression is a goal, the optimal PSAdt threshold for intervention should be greater than 2 years. The appropriate threshold is likely about 3 years. That constituted 22% of patients in this series.

Patient selection

Many authors have attempted to identify insignificant prostate cancer based on PSA and biopsy criteria. All have used the Stamey definition of < 0.5 cc of low-grade cancer. This was empirical. The incidences vary widely, from up to 30% in T1C patients as reported by the Johns Hopkins group[18-20] to values as low as 9%-12% in other series.[21-23] Contemporary radical prostatectomy series report insignificant prostate cancer in 5.8% to 26% of the specimens.[4,23-26] Crucially, the designation of 'insignificant' disease is based on histological volume, not natural history. It is likely, in view of the epidemiologic data, that many patients with more substantial volume of disease have 'insignificant' prostate cancer. A summary of these criteria are in Table 2.

Future plans

This is a phase II cohort with 8-year follow up. The natural history of prostate cancer mandates longer follow up. Our study is ongoing, and will provide more information about the outcome of this selective approach to treatment as it matures.

The approach of active surveillance with selective delayed intervention requires validation in a prospective randomized trial. The Standard Treatment Against Restricted Treatment (START) trial will randomize patients between this approach and whichever local therapy the patient selects (surgery, brachytherapy, or external beam irradiation). This trial is currently in the development stage, and our hope is that it will be implemented as an international intergroup trial.

Conclusion

Watchful waiting (with palliative intent only) is clearly appropriate for patients who are elderly, have significant co-morbidity, and have favorable clinical parameters. The use of co-morbidity indices facilitates the identification of patients whose life expectancy is diminished relative to the natural history of their prostate cancer. The likelihood of a prostate cancer death in these patients is low.

Many good risk young, healthy patients, however, fall into a grey zone where there may be benefits of curative treatment, particularly if they have more biologically aggressive disease than suspected by their clinical parameters. In these patients, a policy of close monitoring with selective intervention for those who progress rapidly is appealing. This approach is currently the focus of several clinical trials and preliminary analysis of these has demonstrated that it is feasible. Most patients, who understand the basis for this approach, will remain on observation long term. If patients are selected properly (good risk and low volume disease) and followed carefully (with

early intervention for evidence of progression), it is likely that the majority with indolent disease will not suffer from it, and the minority with aggressive disease will still be amenable to cure. Thus, almost all will die of non-prostate cancer causes. □

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