Published in final edited form as:

BJU Int. 2011 May ; 107(10): 1582–1586. doi:10.1111/j.1464-410X.2010.09652.x.

Watchful waiting for localized prostate cancer in the PSA era: what have been the triggers for intervention?

John J. Coen, Adam S. Feldman*, Matthew R. Smith†, and Anthony L. Zietman

Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

* Department of Urology, Massachusetts General Hospital, Boston, MA, USA

† Department of Medical Oncology, Massachusetts General Hospital, Boston, MA, USA

Abstract

OBJECTIVE—

- To report outcomes for patients with localized prostate cancer managed using a watchful waiting strategy at an American centre and to explore factors that have triggered intervention.

PATIENTS AND METHODS—

- From 1991 to 2005, 218 patients diagnosed with untreated localized prostate cancer were followed at Massachusetts General Hospital with prostate-specific antigen (PSA) monitoring and digital rectal examination (DRE). Re-biopsies were performed in 95 of the patients.
- The median follow-up was 6.3 years. Clinical outcomes and features predicting intervention were examined.

RESULTS—

- At diagnosis, the median PSA level was 5.4 ng/mL. The Gleason score (GS) distribution was as follows: 95% with GS 6, 4% with GS 7, 1% with GS 8. The clinical T-stage distribution was as follows: 6% with T1a–b, 84% with T1c, 10% with T2. The median age was 71 years.
- At 10 years, the overall survival was 79%, the cause-specific survival was 100%, the rate of distant metastasis was 5%, the rate of salvage androgen deprivation therapy was 15% and the rate of freedom from intervention (FFI) was 70%.
- There was a PSA velocity of ≥ 2 ng/mL per year in 16% of patients, and a PSA doubling time of ≤ 3 years in 15% of patients.
- Among the 95 re-biopsied men, the GS increased (grade progression) in 25% and the percentage of positive cores increased (volume progression) in 33%.
- On multivariate analysis, only PSA doubling time and volume progression were independent predictors of FFI.

CONCLUSIONS—

Correspondence: John J. Coen MD, Department of Radiation Oncology, Massachusetts General Hospital, 100 Blossom St, Cox 3, Boston, MA 02114, USA. jcoen@partners.org.

CONFLICT OF INTEREST

None declared.

- In the present series, watchful waiting was associated with low rates of intervention and cancer progression.
- As PSA doubling time and volume progression were the main triggers for intervention, these will be incorporated into the centre's current active surveillance protocol.

Keywords

prostate cancer; watchful waiting; active surveillance; PSA

INTRODUCTION

Most patients diagnosed with prostate cancer in the PSA era have features suggesting low-risk disease. 'Watchful waiting' was commonly used in the 1970s and 1980s (the pre-PSA era) and was an approach that deferred treatment, usually hormonal therapy, until the disease became symptomatic, if ever. More recently, this has evolved into the approach known as 'active surveillance', where time is used as a prognostic test and curative therapy initiated when predetermined signs of progression become evident.

The 1990s and the first half of the last decade were a long period of transition between the two approaches. During that time the uncertainty meant that this approach tended to be reserved for elderly patients and those with substantial co-morbidities. This also represents a period in which differing physician approaches allowed the collection of data on true predictors of progression and on predictors of treatment initiation by physicians. These are not necessarily the same thing. Several series from the UK and Canada have reported low rates of progression and intervention with 20–30% of patients ultimately receiving active treatment [1,2]. Those reported from the USA appear to have higher rates of intervention, on the order of 57–73% [3,4]. Whether this results from a higher progression rate, closer surveillance or a lower trigger threshold for therapy is unclear.

In the present study, we report on a single USA institution's experience with watchful waiting and explore factors that triggered therapeutic intervention. Because the study reaches back to the 1990s, before the concept of active surveillance was formalized, it explores how patients were managed in the 'PSA era' before strict criteria for intervention were established.

PATIENTS AND METHODS

In the present retrospective analysis, we examined the database developed and maintained at Massachusetts General Hospital with the approval of the institutional review board. Patients were identified either from follow-up lists maintained by the managing physicians or by screening billing records from the Department of Radiation Oncology for patients with a diagnosis of prostate cancer who were followed for at least a 6-month interval before receiving treatment or who were followed without ever receiving treatment.

Between 1991 and 2005, 218 patients were diagnosed with localized prostate cancer and elected or recommended for watchful waiting as the primary management strategy. All patients have a follow-up of at least 3 years. None received primary radiation or prostatectomy, while 13 received a brief course of hormonal therapy for a median (range) time of 3 (3–6) months. Patients were followed up at approximately 6-month intervals with serial PSAs and DREs. The median (range) number of follow-up PSAs was eight (1–56). Re-biopsies were performed at the discretion of the managing physician, as there was no formal protocol, and were carried out in 95 patients. The number of re-biopsies performed in these 95 patients ranged from one to seven, with 59 patients having only one re-biopsy. The

median (range) follow-up was 6.3 (3.1–18.1) years. Intervention with treatment was at the discretion of the managing physician and the patient, as there were no formally established ‘triggers’ over this period of time.

ENDPOINTS

The endpoints assessed included overall survival, disease-specific survival, distant metastasis-free survival, freedom from intervention (FFI) and freedom from salvage androgen deprivation therapy. A secondary analysis performed in patients who had undergone a re-biopsy assessed freedom from progression (FFP), where progression was defined as PSA doubling time of <3 years, Gleason score (GS) of 4 + 3 on re-biopsy, metastatic disease, death from prostate cancer or intervention for any reason.

PSA KINETICS

The PSA velocity was calculated as the slope of PSA over time using linear regression. PSA doubling time was calculated as the inverse of the slope of log(PSA) over time.

STATISTICS

Actuarial analysis was performed using the Kaplan–Meier method. Differences between curves were assessed using the log-rank method. The chi-squared test was used to compare proportions among population sub-groups. The Cox proportional hazards model was used to perform multivariate analysis.

RESULTS

The tumour and patient characteristics of the present group of patients are shown in Table 1. Most patients had low-risk features: 90% with T1, 95% with GS ≤ 6 and 90% with initial PSA level <10 ng/mL. The median (range) PSA level was 5.4 (0.5–25.1) ng/mL. The median (range) age was 71 (46–85) years. Many patients had significant co-morbidities, as shown in Table 2.

Overall survival rates were 94 and 79% at 5 and 10 years, respectively. Of the 29 deaths, two were due to prostate cancer. As both of these occurred beyond 10 years, the prostate cancer-specific survival rate was 100% at both 5 and 10 years. Four patients developed distant metastasis. The rates of freedom from distant metastasis were 99 and 95% at 5 and 10 years, respectively, and FFI rates were 85 and 70% at 5 and 10 years, respectively (Fig. 1). Among the 48 patients receiving treatment, the type of treatment administered was as follows: radical prostatectomy in three (6%), external radiation in 31 (65%), brachytherapy in four (8%) and hormonal therapy in 10 (21%). Salvage androgen deprivation therapy was initiated in 12 patients. Rates of freedom from androgen deprivation therapy were 99 and 85% at 5 and 10 years, respectively.

A multivariate analysis using the Cox proportional hazards model and stepwise selection was performed for overall survival which included all co-morbidities occurring in at least 5% of the present patient cohort (see Table 2), in addition to age (< or >75 years), initial PSA level (< or >10 ng/mL), T stage and GS ($\leq$ or >6). The final model included only advanced age ($P = 0.02$) and presence of diabetes mellitus ($P = 0.003$) as predictors of death. A similar analysis was performed for FFI and the final model included only T stage ($P \leq 0.001$).

A secondary analysis was performed in the 95 patients who underwent prostate re-biopsies. The GS increased in 25%; it increased to GS 4 + 3 or greater in 11%. An effort was made to

assess cancer volume progression as a function of the percentage of the cores that contained cancer at re-biopsy vs the initial diagnostic biopsy. If the percentage of positive cores increased by a quartile (i.e. from 0–25% to 25–50%) or more, that was considered volume progression in this analysis. By this measure, there was volume progression in 33% of re-biopsied patients at some point over their re-biopsy history (some had multiple re-biopsies).

The PSA kinetics were assessed in 194 patients with at least three follow-up PSAs. The median (range) PSA velocity was 0.4 (–3–21.3) ng/mL per year. A PSA velocity ≥ 2 ng/mL per year was documented in 16% of patients. The median (range) PSA doubling time was 8.4 (0.7–416) years. The PSA doubling time was < 3 years in 15% of men.

In a univariate analysis, PSA velocity, PSA doubling time, grade progression and volume progression all predicted for FFI (see Table 3). When all four variables were included in a multivariate analysis using stepwise selection, only PSA doubling time ($P < 0.001$), and volume progression ($P = 0.002$) were included in the final model.

Progression was defined according to the criteria developed by Klotz [5] and Zhang *et al.* [6]. These criteria include PSA doubling time < 3 years and GS of $4 + 3$ on a re-biopsy. Patients treated without meeting these criteria were censored at the time of intervention. The FFP rates by this definition were 89 and 73% at 5 and 10 years, respectively.

DISCUSSION

In the present PSA-era cohort study from a large single institution, ‘watchful waiting’ for patients with low-risk localized prostate cancer was associated with low rates of cancer progression and treatment intervention. At 10 years, the prostate cancer-specific survival rate was 100%, and the rate of freedom from distant metastases was 95%. There was also a low rate of salvage androgen deprivation therapy, which is a meaningful endpoint in this population. If active treatment averts hormonal therapy, it could be considered beneficial even if it is not shown to avert overt clinical signs of disease, as patients would be spared the morbidity of long-term androgen deprivation and its sequelae. The data in the present study suggest that this risk is, in fact, quite low. This is distinct from the observation series published by Albertsen *et al.* [7] in which, ultimately, over 50% of patients required androgen deprivation. The lower rate in the Massachusetts General Hospital series is probably due, in part, to shorter follow-up but also to more discriminating selection of patients at low risk for progression.

Diabetes and advanced age were both predictive of death in the present series, but neither was associated with a lower likelihood of active treatment. This suggests that patients and physicians could under-estimate the influence of age and common co-morbidities on longevity, and over-estimate the clinical significance of a low-risk prostate cancer in elderly patients with marked co-morbidities. Physician estimates of survival have been shown to be overly optimistic in a variety of clinical situations, including the active treatment of patients with localized prostate cancer [8–11]. Our data suggest this could also be the case in patients not treated but followed by watchful waiting for low-risk prostate cancer.

The PSA doubling time and volume progression on repeat biopsy were the primary triggers for intervention in this series. Patients with GS progression received intervention in most cases as well. Efforts to define appropriate prospective triggers for intervention should include all three of these events as triggers for intervention.

Although there were no pre-defined triggers for intervention for patients in the present retrospective series, it is notable that the actuarial rate of FFI intervention was similar to the rate of FFP as defined by the Klotz criteria (85 vs 89% at 5 years). These criteria include

clinical progression, PSA doubling time <3 years or GS of 4 + 3 or greater on a re-biopsy. The FFP and FFI rates in the present study are higher than those reported by Choo *et al.* [12] in a prospective study using these same triggers for selective intervention. They reported FFI and FFP rates of 48 and 67% at 4 years, respectively. Patients in the present series were older and had predominantly low-risk disease, which probably accounts for most of this difference. Still, this suggests a suitable population of patients with low-risk disease is being followed carefully and treated only when they exhibit reasonable indications of disease progression. Although these indications were not prospectively defined, the present analysis suggests that PSA doubling time and cancer volume progression were the primary triggers for intervention. This is in remarkable contrast to most other American series, where rates of intervention have ranged from 57–73% by 5 years [3,4]. Such high rates of intervention were probably provoked by patient or physician anxiety rather than by cancer progression and led to a pessimism that active surveillance could ever take hold in the USA. Expectant management appeared, therefore, to be treatment deferred rather than avoided. The data in the present study suggest that it can, and most selected men can be kept free from treatment for at least 10 years. Recent data from CaPSURE, the US based national prostate cancer registry, suggest that the proportion of American men being managed expectantly, while still small, has increased over the last 6 years [13].

Most men with low-risk prostate cancer are at little risk of disease progression or death from prostate cancer even without treatment. The present study reviews the intuitive triggers that physicians were using before the last 5 years when active surveillance became better formalized. PSA was the principal driver of treatment and, using this, cancer mortality rates were very low over the period of observation. We believe that efforts to define meaningful triggers for intervention more clearly could increase the number of appropriate patients following and adhering to this strategy in the USA. Support groups and tailored education efforts should also play a role. There is evidence that patients who are better educated regarding the treatment options available to them experience higher degrees of patient satisfaction after active treatment for localized prostate cancer [14–16]. This is probably true for patients pursuing active surveillance as well. There is a perception among US physicians that patients pursuing active surveillance carry an undue psychological burden, as do their families. Data from the UK and the Netherlands suggest that this is not the case in appropriately selected patients [17,18]. This burden is probably less when patients are being followed with well-defined criteria and are appropriately educated and supported.

A well-designed active surveillance strategy should include frequent PSA monitoring and serial prostate re-biopsies. The primary triggers for intervention in the present study included PSA doubling time and cancer volume progression on re-biopsy. When using PSA doubling time as a trigger for intervention, it is critical to obtain frequent PSA values to avoid being over-concerned about random rises that occur from biological variability in the serum values. Serial biopsies are also an essential component to any active surveillance strategy. Criteria for intervention should include some measure of cancer volume progression in addition to GS progression.

In addition to monitoring prostate cancer progression, a sensible active surveillance programme should also incorporate assessment of a patient's evolving co-morbidities. Although most active surveillance protocols and most wise clinicians respect advancing age as a reason to avert aggressive treatment as well as intrusive follow-up for a disease with a declining significance in the face of advancing age, less attention is paid to the accumulation of co-morbidities in younger patients with no greater overall health. The defined triggers for intervention and frequency of follow-up studies should be tailored to an appropriate measure of a patient's co-morbidities.

In conclusion, in the period before formalized active surveillance, patients with low-risk prostate cancer managed by watchful waiting had low rates of cancer progression and treatment intervention. At 10 years, the prostate cancer-specific survival rate was 100% and the rate of freedom from distant metastases was 95%. The PSA doubling time and volume progression on re-biopsy were the primary triggers for intervention in this series. Formal active surveillance programmes should incorporate a strategy for re-biopsy, serial PSA monitoring and an ongoing assessment of the risk posed by a patient's prostate cancer which is tailored to both his age and his overall health status.

Abbreviations

FFI	freedom from intervention
FFP	freedom from progression
GS	Gleason score

References

1. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol.* 2010; 28:126–31. [PubMed: 19917860]
2. Hardie C, Parker C, Norman A, et al. Early outcomes of active surveillance for localized prostate cancer. *BJU Int.* 2005; 95:956–60. [PubMed: 15839912]
3. Zietman AL, Thakral H, Wilson L, Schellhammer P. Conservative management of prostate cancer in the prostate specific antigen era: the incidence and time course of subsequent therapy. *J Urol.* 2001; 166:1702–6. [PubMed: 11586206]
4. Carter CA, Donahue T, Sun L, et al. Temporarily deferred therapy (watchful waiting) for men younger than 70 years and with low-risk localized prostate cancer in the prostate-specific antigen era. *J Clin Oncol.* 2003; 21:4001–8. [see comment]. [PubMed: 14581423]
5. Klotz L. Active surveillance for favorable risk prostate cancer: what are the results, and how safe is it? *Semin Radiat Oncol.* 2008; 18:2–6. [PubMed: 18082582]
6. Zhang L, Loblaw A, Klotz L. Modeling prostate specific antigen kinetics in patients on active surveillance. *J Urol.* 2006; 176:1392–7. [PubMed: 16952640]
7. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA.* 2005; 293:2095–101. [PubMed: 15870412]
8. Lamont EB, Christakis NA. Prognostic disclosure to patients with cancer near the end of life. *Ann Intern Med.* 2001; 134:1096–105. [see comment]. [PubMed: 11412049]
9. Chow E, Davis L, Panzarella T, et al. Accuracy of survival prediction by palliative radiation oncologists. *Int J Radiat Oncol Biol Phys.* 2005; 61:870–3. [PubMed: 15708268]
10. Walz J, Gallina A, Perrotte P, et al. Clinicians are poor raters of life-expectancy before radical prostatectomy or definitive radiotherapy for localized prostate cancer. *BJU Int.* 2007; 100:1254–8. [PubMed: 17979925]
11. Mohan R, Beydoun H, Barnes-Ely ML, et al. Patients' survival expectations before localized prostate cancer treatment by treatment status. *J Am Board Fam Med.* 2009; 22:247–56. [see comment]. [PubMed: 19429730]
12. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. *J Urol.* 2002; 167:1664–9. [PubMed: 11912384]
13. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol.* 2010; 28:1117–23. [PubMed: 20124165]

14. Clark JA, Bokhour BG, Inui TS, Silliman RA, Talcott JA. Measuring patients' perceptions of the outcomes of treatment for early prostate cancer. *Med Care*. 2003; 41:923–36. [PubMed: 12886172]
15. Clark JA, Inui TS, Silliman RA, et al. Patients' perceptions of quality of life after treatment for early prostate cancer. *J Clin Oncol*. 2003; 21:3777–84. [PubMed: 14551296]
16. Hu JC, Kwan L, Saigal CS, Litwin MS. Regret in men treated for localized prostate cancer. *J Urol*. 2003; 169:2279–83. [PubMed: 12771770]
17. Burnet KL, Parker C, Dearnaley D, Brewin CR, Watson M. Does active surveillance for men with localized prostate cancer carry psychological morbidity? *BJU Int*. 2007; 100:540–3. [PubMed: 17550414]
18. van den Bergh RC, Essink-Bot ML, Roobol MJ, et al. Anxiety and distress during active surveillance for early prostate cancer. *Cancer*. 2009; 115:3868–78. [PubMed: 19637245]

FIG. 1.
Freedom from intervention.

TABLE 1Patient characteristics ($N = 218$)

Variable	Median (range) or n (%)
Age, years	71 (46–85)
PSA, ng/mL	5.4 (0.5–25.1)
GS	
≤6	206 (95)
7	9 (4)
8	3 (1)
T stage	
1a–b	12 (6)
1c	183 (84)
2	22 (10)

TABLE 2

Co-morbidities

	Number (%)
AIDS	2 (1)
Other cancer	34 (16)
Cardiovascular	98 (45)
Diabetes mellitus	32 (15)
Dementia	3 (1)
Endocrine	9 (4)
Gastrointestinal	31 (14)
Haematological	6 (3)
Hepatic	3 (1)
Hyperlipidaemia	71 (33)
Hypertension	104 (48)
Neurological	13 (6)
Psychological	9 (4)
Renal	11 (5)
Pulmonary	25 (12)

TABLE 3

Triggers for intervention

	Number	FFI at 8 years	Log-rank <i>P</i> -value
PSA velocity, ng/mL per year			
≥2	31	56%	0.002
<2	163	81%	
PSA doubling time, years			
≤3	29	51%	<0.001
>3	165	82%	
GS progression			
Yes	23	36%	0.0003
No	68	82%	
Cancer volume progression			
Yes	30	40%	<0.001
No	61	86%	