Active surveillance with selective delayed intervention: walking the line between overtreatment for indolent disease and undertreatment for aggressive disease

Laurence H. Klotz, MD

Division of Urology, Sunnybrook & Women's College Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

KLOTZ LH. Active surveillance with selective delayed intervention: walking the line between overtreatment for indolent disease and undertreatment for aggressive disease. The Canadian Journal of Urology. 2005;12(Supp 1):53-57.

Purpose: *To summarize the case for active surveillance for good risk prostate cancer with selective delayed intervention for rapid biochemical or grade progression, and review the results of a large phase II experience using this approach.*

Materials and methods: *A prospective phase II study of active surveillance with selective delayed intervention was initiated in 1995. Patients were managed initially with surveillance; those who had a PSA DT of 2 years or less, or grade progression on rebiopsy were offered radical intervention. The remainder were closely monitored.*

Results: *The cohort consists of 299 patients with good risk prostate cancer, or intermediate risk prostate cancer in men over 70. The median PSA doubling time was 7.0 years. 35% had a PSA DT > 10 years. The majority of patients remain on surveillance. At 8 years, overall actuarial survival is 85%, and disease specific survival is 99%.*

Conclusion: *Most men with favorable risk prostate cancer will die of unrelated causes. The approach of active surveillance with selective delayed intervention based on PSA DT represents a practical compromise between radical therapy for all (which results in overtreatment for patients with indolent disease), and watchful waiting with palliative therapy only (which results in undertreatment for those with aggressive disease). The results at 8 years are favorable. Longer follow up will be required to confirm the safety of this approach in men with a long (>15 year) life expectancy.*

Key Words: prostate cancer, active surveillance, PSA doubling time

Introduction

Localized prostate cancer is overtreated, in that some patients not destined to suffer prostate cancer death or morbidity are subject to radical therapy.[1-8] Several recent studies have driven this point home forcefully. The PCPT study reported a 25% positive biopsy rate in the placebo arm; most of these men had a normal PSA.[9] This proportion is consistent with the number of men who harbor prostate cancer detected at autopsy.[10] Since the chance of dying of prostate cancer historically is about 2.5%, this suggests that approximately 10 times as many men will be diagnosed by routine biopsy as will die of the disease. Presumably, the risk of death in good risk patients is considerably lower than this. Stamey[11] has recently reported that the correlation between prostate cancer volume and PSA has fallen steadily, from 0.6 to about 0.02, over the last 20 years. This suggests that in most

Address correspondence to Dr. Laurence H. Klotz, Division of Urology, Sunnybrook & Women's College Health Sciences Centre, 2075 Bayview Avenue # MG 408, Toronto, Ontario M4N 3M5 Canada

men with mild PSA elevation (<10) in a screened population, the PSA is unrelated to cancer. Therefore, a fundamental research objective in this disease is to enhance prediction of the biologic phenotype of the cancer. One method to do this is to use the window of curability that exists for patients with favorable risk disease to estimate the biological aggressiveness of the tumor based on PSA doubling time.

Results of active surveillance with selective intervention approach

We have conducted a clinical study to evaluate a novel approach in which the choice between a definitive therapy and conservative policy is determined by the rate of PSA increase or the development of early, rapid clinical and/or histologic progression.[13-21] This strategy offers the powerful attraction of individualizing therapy according to the biological behavior of the cancer. Patients with slowly growing malignancy would be spared the side effects of radical treatment, while those with more rapidly progressive cancer would still benefit from curative therapy.

This prospective study consisted of 299 patients followed with active surveillance with selective delayed intervention. Patients had PSA of <15, Gleason <=7, and T<=2b. The grade, stage, and PSA of the study population is summarized in Table 1. After obtaining informed consent, patients were followed with active surveillance until they met specific criteria defining rapid or clinically significant progression. These criteria were as follows:

1. PSA progression, defined by all of the following three conditions:
   (a) PSA doubling time < 2 years, based on at least three separate measurements over a minimum of 6 months
   (b) Final PSA > 8 ng/ml
   (c) P value < 0.05 from a regression analysis of ln (PSA) on time
2. Clinical progression when one of the following conditions was met:
   (a) More than twice increase in the product of the maximum perpendicular diameters of the primary lesion as measured digitally
   (b) Local progression of prostate cancer requiring TURP
   (c) Development of ureteric obstruction
   (d) Radiological and/or clinical evidence of distant metastasis
3. Histologic progression: Gleason score $\geq$ 8 in the rebiopsy of prostate at 12-18 months.

Most of the patients in this series fulfilled the criteria for favorable disease (PSA < 10, Gleason $\leq$ 6, T $\leq$ 2a). Eighty percent of patients had Gleason 6 or less, and 78% had a PSA < 10. With a median follow up of 55 months, 60% remain on surveillance. Of the patients coming off surveillance, 12% of patients came off because of rapid biochemical progression; 8% for clinical progression; 4% for histologic progression; and 16% due to patient preference.

Overall survival is 85% at 8 years Figure 1 and disease specific survival 99% at 8 years Figure 2. Of the two patients who died of prostate cancer, both died 5 years after diagnosis.

The distribution of PSA doubling times (PSA dt) is seen in Figure 1, and the cumulative distribution in Figure 3. The median PSA dt was 7.0 years. Only 21% of patients had a PSA doubling time < 3 years. Forty two percent had a PSA DT > 10 years.

Patients were re-biopsied 1.5-2 years after being placed on the surveillance protocol. Grade remained stable in 92%; only 8% demonstrated significant (> 2 Gleason score) rise. This is also consistent with the recent publication by Epstein and Walsh,[29] demonstrating a 4% rate of grade progression over

TABLE 1. **Clinical parameters of 299 patients on active surveillance**

	Clinical Stage						
	T1b - T1c (n=125)			T2a - T2c (n=75)			
Grade/PSA	**<5**	**5 - 9.9**	**10 - 14.9**	**<5**	**5 - 9.9**	**10 - 14.9**	**Total**
Gx*	0	0	0	1	2	0	3
2 – 4	4	4	3	0	0	0	11
5	11	19	5	7	9	0	51
6	48	60	14	19	18	18	177
7	3	12	10	10	15	7	57
Total	66	95	32	37	44	25	299

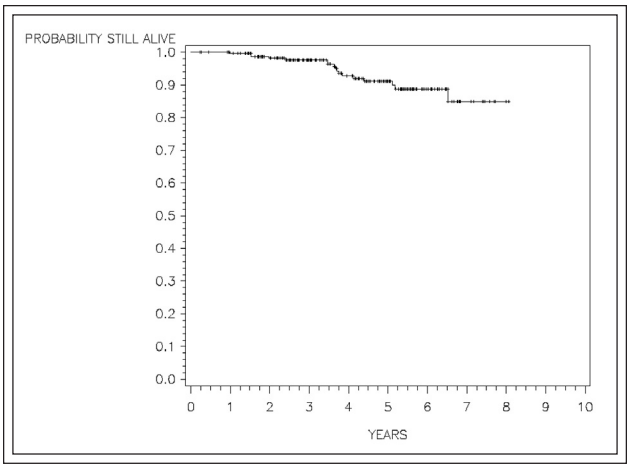

Figure 1. Overall survival on the TSRCC surveillance cohort (n=299).

2-3 years.

Neither grade, stage, baseline PSA, or age correlated significantly with the PSA DT. Only a fall in the PSA free/total ratio correlated with a rapid PSA DT.[35] Patients were followed with serial bone scans. None of the patients, including the rapid PSA DT cohort, manifested a positive bone scan during the duration of the study.[33] Analysis of the TRUS data (performed every 6 months for 2 years, and then annually) showed no correlation between TRUS and rapid biochemical progression.[37]

Twenty-four patients (of 299) had a radical prostatectomy after they manifested a PSA doubling time of less than 2 years. All had Gleason 5-6, PSA <10, pT1-2 at study entry. Final pathology was as follows: 10/24 (42%) were pT2, 14 (58%) were pT3a-c, and two (8%) were N1. our series, that

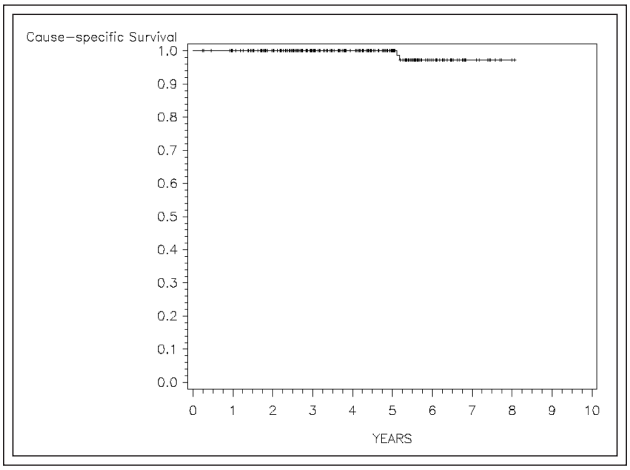

Figure 2. Prostate cancer specific survival in the TSRCC surveillance cohort (n=299).

constituted 22% of patients.

Discussion

A disease specific survival of 99% at 8 years is encouraging. Longer follow up is required to address the impact of the delay in therapy for patients with rapid progression. Nonetheless, the fact that the only two prostate cancer deaths have occurred within 5 years of diagnosis is important. In the context of the natural history of prostate cancer, the likelihood is that these patients had occult metastatic disease at the time of diagnosis, in which case earlier treatment would not have been likely to alter the outcome.

In spite of favorable clinical characteristics, the patients with a PSA DT < 2 years had a relatively high rate of locally advanced disease (58%). This supports the view that a short PSA DT is associated with a more aggressive phenotype. A PSA DT < 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 PSA DT threshold for intervention should be somewhat greater than 2 years. A rough approximation is that the optimal threshold is about 3 years.

Stamey has recently observed that the correlation between PSA and prostate cancer volume has declined since the advent of PSA screening. Benign prostatic volume, rather than prostate cancer, is therefore the

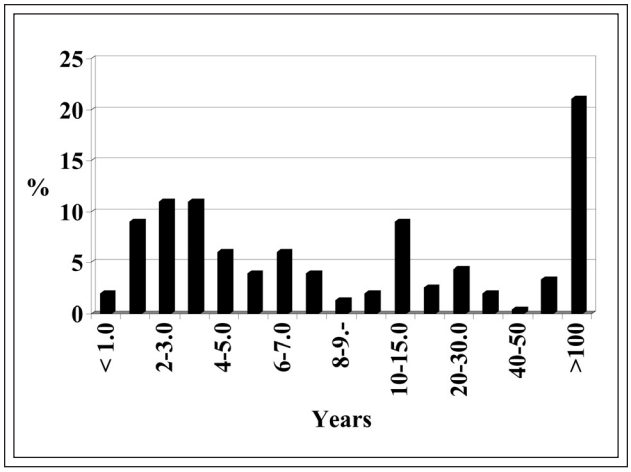

Figure 3. Doubling times of PSA in 299 patients on an active surveillance protocol. The data is based on a median follow up of 55 months. Median PSA doubling time was 7.00 years.
Median number of measurements was 7 (range 3-19). Twenty-two percent of patients had a PSA DT < 3 years.

cause of mild elevation of PSA (<12) in most men with early prostate cancer. If so, this could confound the identification of rapid PSA progression because the baseline PSA will vary as a function of benign prostatic volume.

One solution to this problem is to subtract the baseline PSA (which presumably reflects a substantial BPH component) from all subsequent PSA determinations in calculating the doubling time. This is based on a three parameter model:

$$PSA = A + BT + Cel^{T}$$

where A=baseline PSA from BPH, B=linear increase of PSA from BPH over time (assumed to be minimal), and C=the exponential increase of PSA from CaP over time.

We applied this model to the patients in this cohort. We restricted the analysis to the 229 patients who had a minimum of seven PSA determinations over 2 years. A subtracted PSA doubling time is, of necessity, either the same or less than the conventionally determined PSA DT. The median PSA DT dropped to 4 years from 7.0 years. Twenty percent of patients had a PSA DT < 1.2 years, and this figure was used to define the rapid risers (subtracted). Twenty-seven of 229 patients (12%) had a slow (>3 years) conventionally determined PSA DT but a rapid (<1.2 years) subtracted PSA DT. The significance of this remains uncertain. These patients are being scrutinized carefully.

Conclusions

The approach of active surveillance with selective intervention for patients with rapid biochemical or clinical progression is appealing for good risk patients. Most patients, who understand the basis for the approach, will remain on observation long term. Doubling time varies widely, and was not predicted by grade, stage, or baseline PSA. Forty-two percent have a PSA doubling time (T_D) > 10 years. Doubling time appears to be a useful tool to guide treatment intervention for patients managed initially with expectant management. A doubling time of less than 2 years appears to identify patients at high risk for local progression in spite of otherwise favorable prognostic factors. It is possible that this subset of patients would have an improved outcome with earlier therapy; this is unknown. Based on this experience, the appropriate threshold for initiation of definitive therapy appears to be a doubling time of around 3 years, and approximately 20% of patients will fall into this category. The remainder have a high chance of remaining free of recurrence and progression for many years. If patients are selected properly (good risk and low volume disease) and followed carefully (with intervention for evidence of rapid PSA or grade progression), it is likely that almost all will die of causes unrelated to prostate cancer. This approach warrants evaluation with a prospective comparative trial. □

References

1. Chodak GW. The management of localized prostate cancer *J Urol* 1994;152(5 Pt 2):1766.
2. Albertsen PC, Hanley IA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA* 1998;280:975-980.
3. Sandblom G, Dufmats M, Varenhorst. Long-term survival in a Swedish population-based cohort of men with prostate cancer. *Urology* 2000;56(3):442-447.
4. Whitmore WF, Warner IA, Thompson IM. Expectant management of localized prostatic cancer. *Cancer* 1991;67:1091-1096.
5. Johansson JE, Holmberg L, Johansson S et al. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. *JAMA* 1997;277:467-471.
6. Hanash KA, Utz DC, Cook EN et at. Carcinoma of the prostate: a 15 year followup. *J Urol* 1972;107:450-453.
7. Handley R, Carr TW, Travis D et al. Deferred treatment for prostate cancer. *Br I Urol* 1988;62:249-253.
8. Adolfsson J, Carstensen J, Lowhagen T. Deferred treatment in clinically localized prostate carcinoma. *Brit J Urol* 1992;69:183-187.
9. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, Minasian LM, Ford LG, Lippman SM, Crawford ED, Crowley JJ, Coltman CA Jr. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. *N Engl J Med* 2004; 350(22):2239-2246.
10. Sakr WA, Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. *J Urol* 1993; 150(2 Pt 1):379-385.
11. Stamey TA, Caldwell M, McNeal JE, Nolley R, Hemenez M, Downs J. The prostate specific antigen era in the United States is over for prostate cancer: what happened in the last 20 years? *J Urol* 2004;172(4 Pt 1):1297-1301.
12. Choo R, DeBoer G, Klotz L, Danjoux C, Morton GC, Rakovitch E, Fleshner N, Bunting P, Kapusta L, Hruby G. PSA doubling time of prostate carcinoma managed with watchful observation alone. *International Journal of Radiation Oncology, Biology, Physics* 2001;50(3):615-620.
13. Choo R, Klotz L, Danjoux C, Morton G. Feasibility study of watchful waiting for localized low to intermediate grade prostate cancer with selective delayed intervention based on PSA, histologic, and/or clinical progression. *Journal of Urology* 2002;167:1664-1669.
14. Do V, Choo R, De Boer G, Klotz L, Danjoux C, Morton G, Szumacher E, Fleshner N, Bunting P. The role of serial free/total prostate-specific antigen ratios in a watchful observation protocol for men with localized prostate cancer. *BJU Int* 2002:89(7):703-709.

15. Yap BK, Choo R, Deboer G, Klotz L, Danjoux C, Morton G. Are serial bone scans useful for the follow-up of clinically localized, low to intermediate grade prostate cancer managed with watchful observation alone? *BJU Int* 2003;91(7):613-617.
16. Klotz L. Expectant management with selective delayed intervention for favorable risk prostate cancer. *Urol Oncol* 2002;7(5):175-179.
17. Bunting PS, DeBoer G, Choo R, Danjoux C, Klotz L, Fleshner N. Intraindividual variation of PSA, free PSA and complexed PSA in a cohort of patients with prostate cancer managed with watchful observation. *Clin Biochem* 2002;35(6):471-475.
18. Klotz LH, Choo R, Morton G, Danjoux C. Expectant management with selective delayed intervention for favorable-risk prostate cancer. *Can J Urol* 2002;9(Suppl 1):2-7.
19. Hruby G, Choo R, Klotz L, Danjoux C, Murphy J, Deboer G, Morton G, Rakovitch E, Szumacher E, Fleshner N. The role of serial transrectal ultrasonography in a 'watchful waiting' protocol for men with localized prostate cancer. *BJU Int* 2001;87(7):643-647.
20. Nam RK, Klotz LH, Jewett MA, Danjoux C, Trachtenberg J. Prostate specific antigen velocity as a measure of the natural history of prostate cancer: defining a 'rapid riser' subset. *Br J Urol* 1998;81(1):100-104.