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Review

Active Surveillance with Selective Delayed Intervention Using PSA Doubling Time for Good Risk Prostate Cancer

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Abstract

Good risk prostate cancer, defined as patients with a Gleason score of 6 or less, PSA <10–15, and T1c–T2a, now constitutes 50% of newly diagnosed prostate cancer. For most of these patients, the disease is indolent and slow growing. There is substantial evidence that it does not pose a threat during the lifetime of most patients. The challenge is to identify those patients who are not likely to experience significant progression while offering radical therapy to those who are at risk. To date, molecular markers have failed to provide sufficiently reliable predictive information to influence decision making. The approach to favorable risk prostate cancer described in this article uses estimation of PSA doubling time (PSA DT) to stratify patients according to the risk of progression. Patients who select this approach are managed initially with active surveillance. those who have a PSA DT of 3 years or less (based on a minimum of 3 determinations over 6 months) are offered radical intervention. The remainder are closely monitored with serial PSA and periodic prostate re-biopsies (at 2, 5, and 10 years). In this series of 299 patients, the median doubling time was 7.0 years. 42% had a PSA DT >10 years, and 20% had a PSA DT >100 years. The majority of patients in this study remain on surveillance. 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).

Keywords: Prostate cancer; Active surveillance; PSA doubling time

1. Introduction

The experience from 18 studies of watchful waiting, and the results of several large randomized trials reported over the last 2 years, has led to the inescapable conclusion that localized prostate cancer is overtreated. This is particularly true for good risk patients. Some patients benefit, but the majority are not destined to die of disease during their lifetime. A fundamental objective in this disease is to characterize the biologic phenotype of the cancer in order to predict the degree of threat it represents to an individual patient. One method to do this is to use the window of curability that exists for patients with favourable risk disease to estimate the biological aggressiveness of the tumour based on PSA doubling time.

2. Background

The Canadian Consensus Conference on Prostate Cancer defines good risk prostate cancer as patients with Gleason score 6 or less, T1c–T2a, and PSA <10. Several studies have suggested that expectant management for good risk disease provides similar 10-year survival rates and quality-adjusted life years compared with radical prostatectomy or radiotherapy [1–8]. Expectant management alone, however deprives some patients with potentially curable life-threatening dis-

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Table 1

Reference	Stage	Year last patient accrued	*N*	Survival		
				5 years	10 yrs	15 yrs
Hanash [3]	A	1942	50	86	52	22
	B		129	19	4	1
Lerner [6]	T1b–T2	1982	279	88	61	
				95 CSS	80 CSS	
Adolfsson [8]	T1–2	1982	122	82	50	
				99 CSS	84 CSS	
Johansson [2]	T1–2	1984	223		41/	21
					86 CSS	81 CSS
Albertsen [15]		1984				
Handley [7]		1985	278			
Waaler [9]	T2	1985	28	94 CSS		
Whitmore [10]	T2	1986	37	95	90	62
George [11]	Tx	1986	120	86	66	66
Aus [12]	T1–4	1991	301	80 CSS	50 CSS	30 CSS
Holmberg [25]	T1–2	1999	348	91 CSS		
				82 OS		

ease of the opportunity for curative therapy. Conversely, radical therapy is overtreatment for many patients with indolent disease.

Estimates from autopsy studies indicate that 30% of men over the age of 50 have prostate cancer [28]. Sakr [18] has indicated that the disease develops in the 30s in the typical patient, and takes 20 years to become clinically detectable. Historically, about 10% of men over 50 years old will have clinical progression of prostate cancer resulting in a diagnosis, and 2.5–3% will die of the disease [29]. Among those with clinically diagnosed prostate cancer, the historic likelihood of death from prostate cancer is one in three to one in four.

Recent data from the European Study of Screening and the PCPT trial indicate that in populations that are heavily screened, the incidence figures change dramatically [30]. In the European screening study, the incidence to mortality ratio increased from 2.5:1 to 17:1, a 7-fold increase. In the PCPT trial, the proportion of normal men on the placebo arm diagnosed with prostate cancer after systematic biopsies was 25%.

This powerful data indicates that our current policy of screening results in a prostate cancer diagnosis in a very substantial proportion of the patients who have 'clinically insignificant', latent prostate cancer. (The term 'clinically insignificant' is being used here in its true sense, meaning patients not destined to suffer disease related morbidity or mortality. This is in contrast to the meaning it has acquired in the prostate cancer literature, referring to minimal pathologic disease. Patients may have substantial disease pathologically by the end of their life, which is clinically insignificant if it hasn't caused any problems.)

A number of observations can be made from the surveillance studies (Table 1) [1–8,9–15]. A meta-analysis of 6 surveillance series comprising 828 patients reported by Chodak indicated that at 10 years, disease specific survival was 87% for well and moderately differentiated cancers, and metastasis free survival was 81% and 58% respectively [17].

Mortality from other causes was common in all cohorts, reflecting the average age of patients at entry. Cause specific survival varied substantially, from 30 to 80% at 15 years, reflecting patient selection (Table 2). There are some important similarities between the studies. All reflect natural history from the pre-PSA era. The stage migration phenomenon of the last decade had not occurred when these studies were carried out. None offered salvage radical therapy. Watchful waiting in these series consisted of androgen deprivation for symptomatic metastases. Confounding issues include the use of aspiration cytology for diagnosis, exclusion of higher risk patients, a trend towards elderly patient cohorts, and inclusion of patients with stage T1a.

Table 2
Prostate cancer mortality in a active surveillance cohort according to grade

Gleason score	Prostate cancer mortality at 15 years (%)
2–4	4–7
5	6–11
6	18–30
7	42–70
8–10	60–87

Patients with low grade prostate cancer, by and large do not die of their disease. AS grade increases, the risk of death also goes up; but for Gleason 6, this remains at only 18 to 30% [15].

One striking feature stands out: the majority of patients with prostate cancer are not destined to die of the disease.

The first randomized trial comparing radical prostatectomy to watchful waiting recently reported a 50% reduction in prostate cancer deaths, although an overall survival benefit has not yet been demonstrated [25]. Cause specific survival in the observation arm was 91% with a median follow up of 6.5 years. The patients in this study were largely accrued in the pre-PSA era. 45% had a PSA >10, 75% were T2, and 30% had Gleason 7 or greater. These patients had, in the aggregate, significantly more advanced disease than the typical candidate for active surveillance: PSA mildly elevated, T1c, with small volume of low grade cancer. These more advanced patients still benefited from surgical intervention. Even in this group, however the number needed to treat to prevent each prostate cancer death was 17! Additionally, prostate cancer deaths, if not prevented, usually occur many years after treatment (median 16 years in the Hopkins series). This is often only a few years before death from other causes is likely. To restate this another way: the Holmberg study, which is (justifiably) widely quoted to support radical intervention, implies that 17 men will be put at risk for the side effects of treatment to spare 1 a prostate cancer death, typically about 16 years later. This proportion, of 1:17 in intermediate risk patients, must give us pause. The Holmberg study confirms that favorable risk patients may not require therapy; and if they do, they likely have a long window of curability.

Since the advent of PSA in 1989, substantial resources have been directed towards the early detection and treatment of prostate cancer. Mortality rates have fallen about 20% during that period [26]. Whether this improvement in mortality is due to these efforts, or to other causes, is the subject of intense controversy. Other factors, including dietary and lifestyle modification, and a trend towards earlier initiation of androgen ablation for recurrent disease, may explain some or all of the fall in mortality. Indeed, Albertsen [16] has demonstrated that the fall in mortality in Connecticut, where screening is uncommon, is equivalent to the reduction in Oregon, a highly screened population. Thus it remains uncertain whether our efforts at early diagnosis and local treatment have resulted in a decline in prostate cancer mortality. If realized, this benefit is likely to occur as a consequence of identifying and treating higher risk patients, whose QALY benefit is greater.

Prostate cancer is typically slow growing. Studies by Pound [19] demonstrate that in patients who fail radical prostatectomy and go on to die of prostate cancer, a median of 16 years elapses from surgery until death. The watchful waiting studies also demonstrate that disease related mortality in populations of prostate cancer patients only becomes substantial after 10 years. It is particularly clear that low grade prostate cancer is associated with low progression rates and high survival rates in the intermediate term.

One indirect piece of evidence supporting the long window of curability can be derived from nomograms predicting the likelihood of biochemical recurrence from PSA, grade, and stage. Using the Kattan nomograms of a patient with T1c prostate cancer and Gleason 6 prostate cancer, with PSA of 5, the 5 year biochemical DFS is 91% [20]. If one were to delay intervention until the PSA reaches 10, the 5 year DFS is still 87%; and with further delay until the PSA is 15, it is 81%. Thus, following such a patient during a period of PSA doubling or tripling is associated with only a 5 to 10% reduction in the risk of progression. These patients, (who represent the worst subset with respect to PSA doubling time), appear to remain highly curable.

The art of the management of localized prostate cancer is to differentiate patients with biologically aggressive disease for whom curative therapy is strongly warranted from those with indolent malignancy for whom conservative management is equally efficacious. A blanket policy of observation for all results in under-treatment for some; similarly a policy of treatment for all results in over-treatment for a subset.

Today, in the PSA era, patients who are managed conservatively are typically still followed with periodic PSA tests. This raises the question: Can treatment of favorable prostate cancer be deferred indefinitely in many, while effective, albeit delayed therapy is offered to those whose PSA progresses rapidly, or who have other evidence of significant progression?

3. 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 [22–24]. This strategy offers the powerful attraction of individualizing therapy according to the biological behaviour of the cancer. This would mean that 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. 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 3 conditions:
   (a) PSA doubling time <2 years, based on at least 3 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 ≥8 in the rebiopsy of prostate at 18 months, 5 years, and 10 years.

Most of the patients in this series fulfilled the criteria for favourable disease (PSA <10, Gleason ≤6, T ≤2a). Eighty percent of patients had Gleason 6 or less, and the same proportion had a PSA <10. 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 eight years, overall survival is 85% at eight years; disease specific survival is 99.3%! 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 (PSA DT) is seen in Fig. 1, and the cumulative distribution in Fig. 2. The median PSA DT was 7.0 years. Twenty one % of patients had a PSA doubling time <3 years. Forty two percent had a PSA DT >10 years.

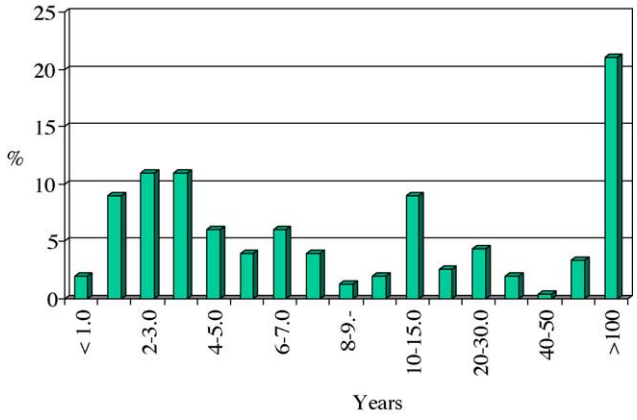

Fig. 1. Doubling times of PSA in 231 patients on an active surveillance protocol. The data is based on a median follow up of 55 months. Median PSA doubling time was 7.00 years. Median number of measurements was 7 (range 3–19). 20% of patients had a PSA DT <3 years.

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 consistent with the Hopkins experience [27], demonstrating a 4% rate of grade progression over 2–3 years.

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

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 favourable clinical features, portents a high likelihood of locally advanced disease. This also suggests that,

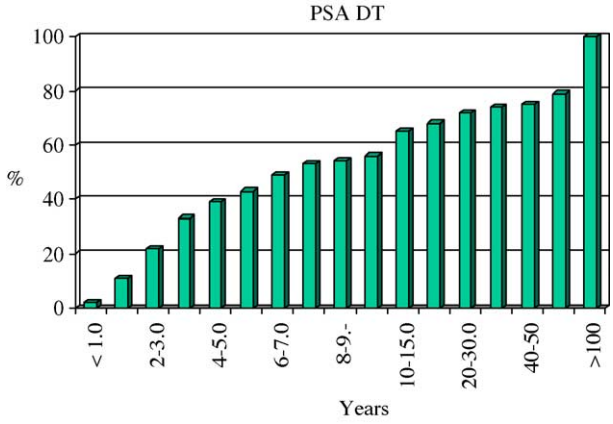

Fig. 2. Cumulative frequency of PSA doubling times.

insofar as cure of the patients with early rapid biochemical progression is a goal, the optimal PSA DT 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.

Zeitman and Schellhammer recently published a retrospective review of 199 men with T1–2 prostate cancer and PSA < 20 ng/ml, managed with active surveillance [21]. Median follow up was 3.4 years. Overall survival at 5 and 7 years was 77% and 63%, and disease-specific survival was 99% at both time points. At 5 and 7 years, the proportion of patients who were alive and untreated was 43% and 26%. 63 patients were treated radically. The median PSA rise from diagnosis to treatment was 2.9 ng/ml in the treated cohort, compared to 0.9 in the untreated group.

This study raised the concern that active surveillance may simply be a version of delayed therapy, unless patients die of co-morbid illness in the interim. However, the indication for intervention in this series was a mild rise in PSA (<3 ng) over a prolonged period. One wonders whether patients panicked as a result of the slow rise in PSA. This emphasizes that conservative management in the modern PSA era requires buy-in by the patient and the doctor. The PSA may progress slowly over time, but slow progression is not a valid reason for intervention.

Additionally, delayed treatment which is still effective, but defers treatment related morbidity, should not be dismissed.

Recently, data from Stamey, the PCPT trial, and the MTOPS trial have pointed to prostatic volume, rather than prostate cancer, as the 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.

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 3 parameter model:

$$\mathrm{PSA} = A + BT + Ce^{\lambda T}$$

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 7 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). 27/229 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. Needless to say, these patients are being scrutinized carefully.

One assumption on which the selective intervention approach is based is that the PSA rate of rise remains relatively stable over time. This is not the case in some patients; rapid rises in PSA after long periods of stability (PSA acceleration) have been clearly documented. The critical unanswered questions with respect to PSA acceleration are: When does it occur in the natural history of prostate cancer? Is this before or after the development of metastatic disease? How common is a sudden rapid increase? How should it be defined? Are patients who manifest PSA acceleration still curable?

4. Conclusions

The approach of active surveillance with selective intervention for patients with rapid biochemical or clinical progression is feasible. 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. 33% 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. The appropriate threshold for initiation of definitive therapy is a doubling time of around 3 years; approximately 20% of patients will fall into this category. The remainder have a high probability 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 progression), it is likely that almost all will die of causes unrelated to prostate cancer.

Active surveillance is clearly appropriate for patients who are elderly, have significant co-morbidity, and have favorable clinical parameters. The use of co-morbidity indices like the ICED facilitate 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 patients, however, fall into a

grey zone where the benefits of treatment are unclear. In these patients, a policy of close monitoring with selective intervention for the 20% who progress rapidly is appealing. This approach is currently the focus of several ongoing clinical trials.

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