Expectant management with selective delayed intervention for favorable-risk prostate cancer

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KLOTZ LH, CHOO R, MORTON G, DANJOUX C. Expectant management with selective delayed intervention for favorable-risk prostate cancer. Supplement of The Canadian Journal of Urology. 2002;9(Supp. 1):2-7.

The optimal management of clinically localized prostate cancer remains unresolved. Management options range from a conservative approach to definitive treatment. While evidence suggests that expectant management yields similar 10-year survival rates and quality-adjusted life years compared to definitive treatment, this approach alone will deprive some patients with potentially curable disease of the opportunity for curative therapy. Effective management of localized prostate cancer requires differentiation between patients with biologically aggressive disease, in whom curative therapy is strongly warranted, and those with indolent malignancy, in whom conservative management would be equally efficacious. A comparison of surveillance studies in the literature yields a striking similarity: every series contains a substantial subset of long-term survivors, particularly in patients with favorable clinical parameters. We describe a prospective clinical study to evaluate a novel approach in which the decision between definitive therapy and conservative management is determined by the rate of prostate-specific antigen (PSA) increase or the development of early, rapid clinical and/or histologic progression. We enrolled 250 patients followed with active surveillance with selective delayed intervention. Patients were followed with active surveillance until they met criteria defining significant PSA, clinical, or histologic progression. At a median follow-up of 42 months, 60 patients came off observation, while 140 have remained on observation. We conclude that an approach of active surveillance with selective intervention for patients with rapid biochemical or clinical progression is feasible, and that PSA doubling time appears useful in guiding intervention in patients managed initially with expectant management. A policy of close monitoring with selective intervention for the 15% who progress rapidly is appealing, and is currently being investigated in several clinical trials.

Key Words: prostate cancer, expectant management, selective intervention, active surveillance, favorable risk

Introduction

The optimal management of clinically localized prostate cancer remains unresolved. Management options are diverse, varying from a conservative approach (expectant management) to definitive treatment (radical prostatectomy or radiotherapy). Several studies have suggested that expectant management provides similar 10-year survival rates and quality-adjusted life years compared with radical prostatectomy or radiotherapy.[1-8] Expectant management alone, however, clearly deprives some patients with potentially curable life-threatening disease of the opportunity for curative therapy. Lu-Yao[9] reported in a population-based study that in particular, patients with a high Gleason score who had undergone radical prostatectomy or radiotherapy had

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improved 5-year overall and disease-specific survival compared with those managed by expectant management alone.

The dilemma of management stems from the heterogeneity of the natural history of prostate cancer. Estimates from autopsy studies indicate that 30% of men over the age of 50 years have prostate cancer. However, only 10% of men over 50 years of age will have clinical progression of prostate cancer resulting in a diagnosis. Among those with clinically diagnosed prostate cancer, the likelihood of death from prostate cancer is one in three. While these statistics suggest a high incidence of "latent" prostate cancer and a slow natural history of prostate cancer in many patients, they also indicate that the risk of dying from clinically diagnosed prostate cancer is substantial. This conundrum is the rationale for both conservative management and radical treatment.

The surveillance studies in the published literature are summarized in Table 1.[1-8,10-16] A number of observations can be made from these studies. Mortality from other causes is common in all cohorts, likely reflecting the average age of patients at entry. Cause-specific survival varies substantially, from 30% to 80% at 15 years. This reflects patient selection at study entry. All reflect natural history from the pre-prostate-specific antigen (PSA) era. The stage migration phenomenon of the last decade had not occurred when these studies were carried out. Secondly, none offered salvage radical therapy for local progression. Watchful waiting in these series consisted of no active treatment until symptomatic metastases developed, at which point androgen ablation was offered. Additionally, these series are characterized to varying degrees by problems of selection bias. Confounding issues include the use of aspiration cytology for diagnosis, exclusion of higher risk patients, elderly cohorts, and inclusion of T1a patients.

Nonetheless, one striking similarity stands out: every series contains a substantial subset of long-term survivors, particularly in the group with favorable clinical parameters. This is a critical observation. In the absence of treatment, a substantial subset of patients with prostate cancer are not destined to die of the disease. The challenge, of course, is to accurately identify that subset.

Rationale for an expectant approach

Since the advent of PSA in 1989, substantial resources have been directed towards the early detection and

TABLE 1. **Surveillance studies in the published literature**

Reference Year	Stage	Year last pt. accrued	N	% survival 5 yrs.	10 yrs.	15 yrs.
Hanash 1972	A	1942	50	86	52	22
Lerner 1991	B	1982	129	19	4	1
Adolfsson 1992	T1b	1982	279	88	61	
Johansson 1997	T2	1984	122	95 CSS	80 CSS	
Albertsen 1998	T1-2	1984	223	82	50	
Handley 1988	T1-2	1985	278	99 CSS	84 CSS	
Waaler 1993	T2	1985	28	94 CSS	41/86 CSS	21/81 CSS
Whitmore 1991	T2	1986	37	95	90	62
George 1988	Tx	1986	120	86	66	66
Aus 1995	T1-4	1991	301	80 CSS	50 CSS	30 CSS

treatment of prostate cancer. Mortality rates have fallen about 20% during that period. 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[17] 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.

The prevalence of prostate cancer far exceeds the incidence. In the PSA era, increasing efforts at screening, and the consequent rise in incidence, has resulted in about 1 of 7 men being diagnosed. As well, the mortality rate has fallen. Thus the chance of dying of prostate cancer in patients who are diagnosed has decreased steadily, from about 1 in 3 to 1 in 5. While this may reflect improved treatment, it may also reflect increased diagnosis of indolent disease.

Prostate cancer is typically slow-growing. Work by Sakr[18] has indicated that the disease develops in the 30s in the typical patient, and takes 20 years to become clinically detectable. 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. In addition, 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 disease-free survival (DFS) is 95%.[20] If one were to delay intervention until the PSA reaches 10, the 5-year DFS is still 90%; and with further delay until the PSA is 15, the 5-year DFS is 85%. Thus, following such a patient during a period of PSA doubling or tripling is associated with a 5% to 10% reduction in the risk of progression.

Widespread use of PSA testing has also resulted in a profound stage migration. Most patients newly diagnosed with prostate cancer have clinically impalpable, stage T1c disease. Additionally, these patients typically have a PSA which is only mildly elevated (< 10). These patients usually have slowly growing cancer with a long window of curability. This is also supported by the Albertson data, Table 2.[16]

A meta-analysis of six 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.[21] These studies also incorporated an "either/or" approach, and reflected a pre-stage migration population. Thus, many patients with favorable prognostic factors, diagnosed considerably earlier in their disease process than the average patient in this surveillance population, are likely to have an incredibly long natural history.

The Prostate Cancer Intervention Versus Observation Trial (PIVOT), comparing radical prostatectomy to watchful waiting, has been an ambitious effort to compare these two approaches in a randomized design.[22] This trial, against all expectations, is close to reaching its accrual target. The outcome will be of profound importance. However, one limitation of the trial is that the observation arm does not have an option for intervention for the subset with evidence of rapid biochemical or local progression early on in the course of the disease.

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 will result in under-treatment for some; similarly a policy of treatment for all will result in over-treatment for a subset.

TABLE 2. **Prostate cancer mortality in a watchful waiting cohort according to grade. Patients with low grade prostate cancer, by and large do not die of their disease. As grade increases, the risk of death also increases; but for Gleason 6, this remains at only 18% to 30%. (Alberston)**

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%

Traditionally, watchful waiting has meant no treatment until progression to metastatic or locally advanced disease, followed by androgen ablation therapy. Today, in the PSA era, patients 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 who progress rapidly?

Watchful waiting with selective intervention: results

We have been conducting 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. This strategy, which has never been previously described or evaluated, offers the powerful attraction of individualizing therapy according to the biological behavior 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 250 patients followed with watchful waiting with selective delayed intervention. Patients had PSA of < 15, Gleason ≤ 7, and T ≤ 2b. Patients were followed with watchful waiting 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 ≥ 8 in the re-biopsy of prostate at 12-18 months

Most of the patients in this series fulfilled the criteria for favorable 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 42 months, 60 patients (30%) came off watchful observation while 140 have remained on surveillance. Of the patients coming off surveillance, 8% came off because of rapid biochemical progression; 8% due to clinical progression; and 8% due to patient preference. The remaining 6% came off surveillance for a variety of other reasons.

The distribution of PSA doubling times is seen in Figure 1. The median PSA doubling time was 10.15 years. Only 20% of patients had a PSA doubling time < 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 also consistent with the recent publication by Epstein and Walsh, demonstrating a 4% rate of grade progression over 2–3 years.

Nine patients (of 200) 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: 3 of 9 were pT2, 5 were pT3a–c, and one was N1. For a group of patients with favorable clinical characteristics, this is a high rate of locally advanced disease. This supports the view that a short PSA doubling time is associated with a more aggressive phenotype. A PSA doubling time < 2 years, in patients with otherwise favorable clinical features, portends a high likelihood of advanced disease. Fortunately, this scenario is uncommon. This also suggests that, insofar as cure of the patients with early rapid biochemical progression is a goal, the optimal PSA doubling time threshold for intervention should be greater than 2 years. The optimal threshold is likely in the range of 3 years. In our series, that constituted 22% of patients.

Zietman and Schellhammer recently published a retrospective review of 199 men with T1-2 prostate cancer and PSA < 20ng/ml, managed with watchful waiting.[23] Median follow-up was 3.4 years. Overall survival at 5 and 7 years was 77% and 63% respectively, and disease-specific survival was 99% and 99% respectively. At 5 and 7 years, the proportion of patients who were alive and untreated was 43% and 26%. Sixty-three 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 ng/mL in the untreated group.

This study raises the concern that watchful waiting

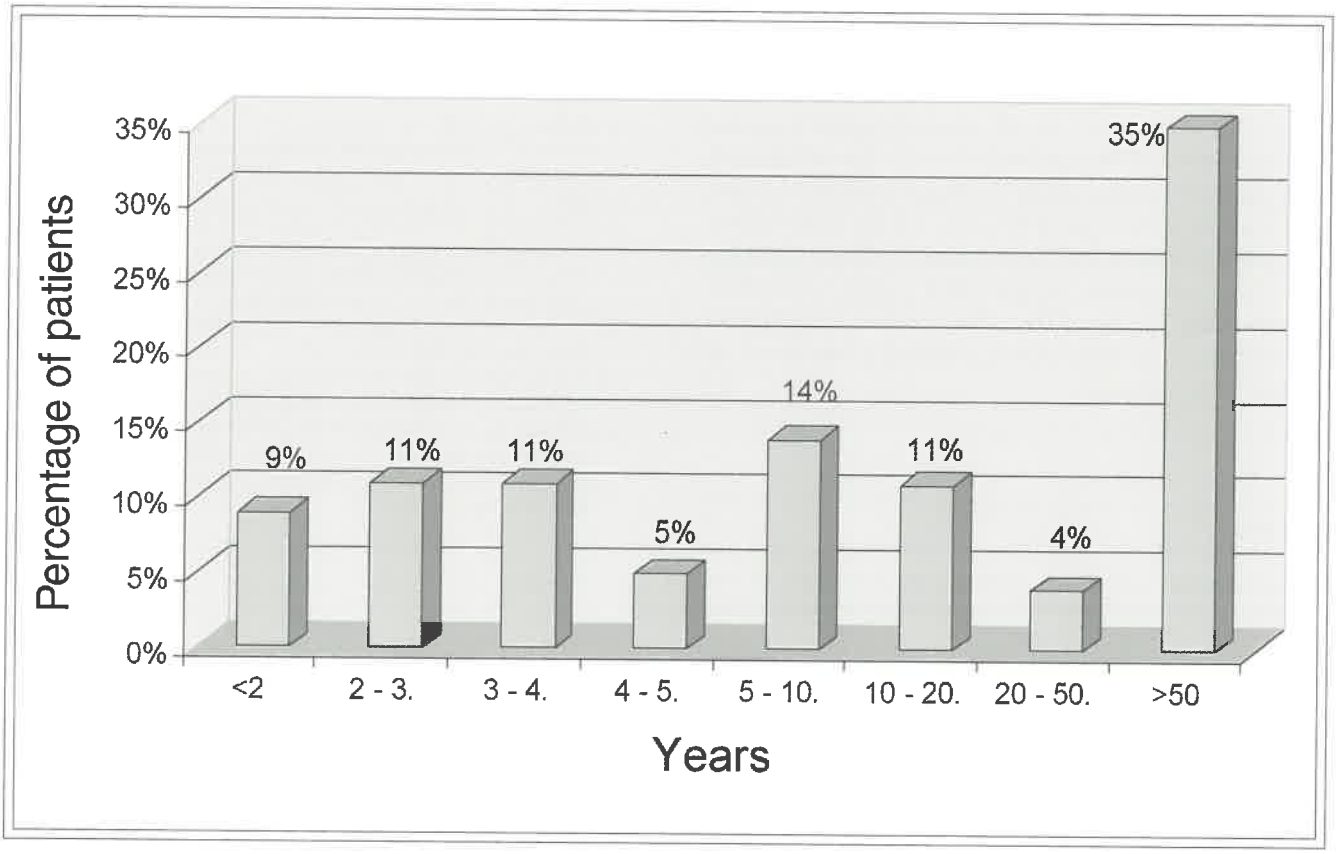

Figure 1. Doubling times of PSA in patients on a watchful waiting protocol. The data is based on a median follow up of 55 months. Median PSA doubling time was 10.15 years. Median number of measurements was 7 (range 3-19). Twenty percent of patients had a PSA doubling time less than 3 years.

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. This emphasizes that conservative management in the modern PSA era requires "buy-in" by the patient and the doctor. This involves an understanding that PSA will likely progress slowly over time, but that slow progression is not a reason for intervention.

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—in particular, relative to the point at which the disease becomes metastatic or locally incurable? How common is a sudden rapid increase? Are patients who manifest PSA acceleration still curable?

Conclusions

The approach of watchful waiting 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. Thirty-three percent have a PSA doubling time greater than 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 chance of remaining free of recurrence and progression for years.

Watchful waiting is clearly appropriate for patients who are elderly, have significant co-morbidity, and

have favorable clinical parameters. The use of co-morbidity indices such as the Index of Co-Existent Disease (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 15% who progress rapidly is appealing. This approach is currently the focus of several clinical trials. □

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