Active surveillance with selective delayed intervention for favorable risk prostate cancer: clinical experience and a 'number needed to treat' analysis

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This is a summary of the case for active surveillance for 'favorable-risk' prostate cancer with selective delayed intervention for rapid biochemical progression, assessed by rising prostate-specific antigen (PSA) levels, or grade progression. The results of a large phase II trial using this approach are reviewed. To date, this study has shown that virtually all men with 'favorable-risk' prostate cancer managed in this fashion will die of unrelated causes. Based on the Swedish randomized trial of radical prostatectomy versus watchful waiting, the Connecticut observation series, and the Toronto active surveillance experience, a number needed to treat analysis of the benefit of radical treatment of all newly diagnosed favorable risk prostate cancer patients, compared to a strategy of active surveillance with selective delayed intervention, is presented. This suggests that approximately 100 patients will require radical treatment for each prostate cancer death averted. This translates into a 2-3 week survival benefit, unadjusted for quality of life. This figure is confirmed based on an analysis of the D'Amico PSA velocity data in favorable risk disease. The approach of active surveillance with selective delayed intervention based on PSADT and repeat biopsy represents a practical compromise between radical therapy for all patients, (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).

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

Introduction

Prostate cancer screening results in diagnosing many men with prostate cancer in whom the disease does not pose a threat to their life. The prevalence of histological prostate cancer in men over 50 years of age is 30%–40%.[1] This is based on autopsy studies of men dying of other causes. A large proportion of this histological, or 'latent' prostate cancer is never destined to progress or affect the lifespan of the patient. Since the introduction of PSA screening, the lifetime risk of being diagnosed with prostate cancer has almost doubled from around 10%, in the pre-PSA era, to 17%.[2-3] An obvious inference is that many cases of localized prostate cancer are over treated, in that some patients not destined to experience prostate cancer death or morbidity are subject to radical therapy.[4-5] A basic challenge in the management of this disease is to improve prediction of the biological phenotype of the cancer.

Cancer aggressiveness can be predicted to some degree using existing clinical parameters. The ones mostly widely used are tumor grade, or Gleason score; PSA; and tumor stage. Many authors have identified favorable risk prostate cancer as Gleason 6 or less, PSA 10 or less, and T1c-T2a disease. As a result of stage migration due to PSA screening, the proportion of newly diagnosed patients who fall into the 'favorable risk' category has increased, and now constitutes

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about 50% of patients. While patients with these characteristics have a much more favorable natural history and progression rate than those with higher Gleason grade or PSA, some of them still progress to advanced, incurable prostate cancer and death.

A recent update of a large group of patients in Connecticut treated with watchful waiting has recently reported 20 year follow-up.[6] This data confirms the powerful predictive value of Gleason score. In that cohort, only 23% of Gleason 6 patients died of prostate cancer at 20 years. For Gleason 7 prostate cancer, about 65% died of prostate cancer. In addition, the author recently subjected the original slides to re-analysis using contemporary Gleason scoring.[7] This demonstrated clearly that there has been a shift in grade interpretation over time. Most Gleason 6 cancers diagnosed 20 years ago would be called Gleason 7 today. Thus the Connecticut results likely represent a 'worse case' scenario.

Autopsy studies have demonstrated that prostate cancer typically begins in the 3rd-4th decade of life. The average age of diagnosis is now around 60. The average age of death from prostate cancer is about 75. This means that, in most patients, there is a period of slow subclinical tumor progression which lasts 20 to 30 years, followed by a period of clinical progression lasting about 15 years. The implication is that most patients have a long window of curability. This is particularly true for patients with favorable risk, low volume disease.

One approach to achieving prediction of tumor aggressiveness is to use this window of curability to estimate the biological aggressiveness of the tumor based on prostate specific antigen doubling time (PSADT).

Traditionally watchful waiting has meant no treatment until progression to metastatic or locally advanced disease, followed by androgen ablation therapy, Table 1.[8-17] Today in the PSA era patients who

TABLE 1. **Summary of watchful waiting series**

Study	Prostate cancer stage	Year the last patient was accrued	Number of patients	Number of patients surviving		
				5 years	10 years	15 years
Hanash et al (1972)[19]	A B	1942	50 129	86 19	52 4	22 1
Lerner et al (1991)[23]	T1b–T2	1982	279	88 95 CSS	61 80 CSS	
Adolfsson et al (1992)[25]	T1-2	1982	122	82 99 CSS	50 84 CSS	
Johansson and Johansson (1997)[21]	T1-2	1984	223		41 86 CSS	21 81 CSS
Albertsen et al (1998)[16]	unknown	1984	767			89–96 Gl ≤5 70–82 Gl 6 30–58 Gl 7 13–40 Gl 8–10
Handley et al (1988)[24]		1985	278			
Waaler and Stenwig (1993)[26]	T2	1985	28	94 CSS		
Whitmore et al (1991)[27]	T2	1986	37	95	90	62
George (1988)[28]	Tx	1986	120	86	66	66
Aus et al (1995)[29]	T1-4	1991	301	80 CSS	50 CSS	30 CSS
Holmberg et al (2002)[62]	T1–2	1999	348	91 CSS 82 OS		

The abbreviations used in the table are as follows: CSS, Cancer-specific survival; Gl, Gleason score; OS, Overall survival

are treated conservatively are followed with periodic PSA tests. This raises the tantalizing prospect that treatment of favorable prostate cancer could be deferred indefinitely in many, while effective, delayed therapy was offered to those in whom PSA progresses rapidly or the tumor grade increases.[18-19]

In the recent large Prostate Cancer Prevention Trial (PCPT) of finasteride as a preventative agent, a strategy of routine systematic biopsies of the prostate was provided to all men in the trial, regardless of PSA level. This was the first time that a large cohort of men with a normal PSA had been subjected to systematic prostatic biopsy. The results, now well known, were astounding. Twenty four percent of patients in the placebo arm were diagnosed with prostate cancer over a 7-year period.[20] This meant, in sharp contrast to accepted wisdom, that routine prostate biopsy, regardless of PSA, results in the detection of latent microfoci of disease in many men. The lifetime risk of dying from prostate cancer remains less than 3%.[3] As the lifetime risk of being diagnosed approaches the known rate of histological (mostly insignificant) prostate cancer, there is a greater risk of over-treatment. At least two studies have attempted to model the rate of diagnosing clinically insignificant disease, suggesting that it ranges from 30% to 84%.[4-5] The current incidence to mortality ratio of about 7:1 suggests that the higher figure is more likely. Factors contributing to this are the increasing use of PSA screening and more extensive biopsy strategies employing 8 to 13 cores.[21] Additionally, biopsies are often repeated until a cancer diagnosis is made.

A large series of patients from Johns Hopkins treated with radical prostatectomy provide one of the best indications of the natural history of prostate cancer.[22] The series showed that a median of 16 years elapses from surgery until death in patients that die of prostate cancer following disease recurrence. Many watchful waiting studies, most of which accrued patients from the pre-PSA era, also demonstrate that disease related mortality in populations of prostate cancer patients only becomes substantial after 10 years. The lead-time afforded by PSA screening is likely to increase this to 15-20 years in screened populations. 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. This is also supported by the Albertson data.[6]

A meta-analysis of six surveillance series comprising 828 patients 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.[23] The updated Connecticut series reported 20 year prostate mortality in Gleason 5 and 6 prostate cancer of 14 and 27% respectively. These studies incorporated an 'either–or' approach (surveillance offered no opportunity for delayed radical local therapy), and were based on a pre-screening population. PSA screening has resulted in a shift towards earlier, smaller volume disease. The estimated lead time between diagnosis based on PSA, and diagnosis based on clinical factors like the Connecticut series has been estimated to be around 10 years by many authors.[24,25] Thus, many patients currently diagnosed by PSA screening, with favorable prognostic factors, are diagnosed considerably earlier in disease development than the average patient in this unscreened population. They are likely to have prostate cancer with an even longer and more benign natural history.

Identifying insignificant disease

In an attempt to define insignificant prostate cancer, Stamey et al studied prostate glands obtained from 139 consecutively sampled radical cystoprostatectomy specimens, of which 55 (40%) had prostate cancer.[26] Since the clinical prevalence of prostate cancer was 8% at the time, the authors concluded that the tumor volumes in the top 92nd percentile (0.5–6.1 ml) were clinically significant. The assumption was that the clinically significant cancer rate was 8%. The arbitrariness of this is of concern. If the clinically significant cancer rate was set at 4%, then the clinically significant cancer volume would be closer to 1 ml; conversely, if it were set at 12% the clinically significant cancer volume would be 0.2 ml. The median age of the patients in the study was 65 years; therefore the applicability of this volume cut-off point to patients much older or much younger than 65 years is limited.

Epstein et a*l*[27] utilized the data from Stamey et al[26] with historical radical prostatectomy cohorts from Johns Hopkins School of Medicine[27-30] to define insignificant cancers as those having clinical stage T1c, tumor volume <0.2 ml, no Gleason pattern of 4 or 5, organ confined disease, and no evidence of seminal vesicle or lymph node invasion. Tumors between 0.2 ml and 0.5 ml were identified as having a minimal risk of progression. Since this classification was developed, other authors have merged these two categories into one, despite the propensity of some of the 0.2 ml–0.5 ml tumors to display capsular invasion, Table 2.[31-37] Using this definition, many groups have

reported on the incidence of insignificant disease. The incidence varies widely, from up to 30% in T1c patients, as reported by the Johns Hopkins group,[27] to values as low as 9%–12% in some of the other series. Contemporary radical prostatectomy series report insignificant prostate cancer in 6% to 26% of specimens. Clinical parameters predicting for minimal disease include Gleason 6 or less, <50% of any 1 core involved, and a maximum of 1-3 cores involved, see Table 2. Crucially, the designation of 'insignificant' disease is based on histological volume, not natural history. The definition of insignificant cancer as <0.5 cc of low-grade disease has never been validated in a trial with a clinical end point. Based on substantial data, including the PCPT trial, and the incontrovertible ratio of 7:1 between the current lifetime likelihood of diagnosis (about 1 in 6) and death (1 in 40), it understates the proportion of patients who have prostate cancer that is not destined to pose a threat to their life (about 6 out of 7).

A recent landmark trial from Sweden recently demonstrated, for the first time, that radical prostatectomy improves survival.[38] In that study, about 600 patients were randomized between radical prostatectomy and watchful waiting. The study showed a 5% absolute survival benefit at 10 years, and a 50% reduction in prostate cancer mortality with surgery.

However, this cohort was a group with pre-stage migration, pre-PSA screening prostate cancer. Only 5% were diagnosed based on PSA screening, and the median PSA was 12.8. Thus it is a reasonable assumption that the volume of disease in these patients represented a pre-stage migration cohort. Even in this group, however, the number needed to treat to prevent each prostate cancer death was 19. This is much different from the current era in a screened population, where a substantial proportion of newly diagnosed patients have small volume low-grade disease. The Swedish study should not be interpreted to mean that all patients with localized prostate cancer should be treated radically. Many studies emphasize that the patients at risk of death from prostate cancer are those with Gleason 4 or 5 pattern cancer.

It is possible to use this data and the Connecticut watchful waiting data to approximate the number of patients with favorable risk prostate cancer that would have to be treated at the time of diagnosis for each prostate cancer death averted at 20 years, compared to the approach of active surveillance with selective delayed intervention. It is possible that with 20-year follow-up, the survival benefit in the Swedish trial will increase. However, this is likely to be balanced by the lead-time inherent in PSA screening. The Albertsen data[6] indicate that the mortality for intermediate risk disease was about 2.5 times greater at 20 years than for favorable risk disease. Thus, about 50 favorable risk patients need to be treated for each death prevented by surgery compared to no treatment. However, if one offers selective delayed intervention to those patients who progress, it is likely that at least 50% can be salvaged. The conclusion is that about 100 radical prostatectomies would be required for each prostate cancer death averted in favorable risk disease. Correcting the Connecticut data for grade migration, as referred to above, would increase this even further. The Pound data suggests that the prostate cancer deaths averted would have occurred on average 16 years after diagnosis, meaning that the number of life years saved in each of these 1 in 100 averted deaths is modest. For the average 60 year old, life would be

TABLE 2. **Clinical parameters to predict 'insignificant' prostate cancer**

Author	PSA density	# Cores positive	Max % of cores pos.	Grade	% Tissue positive	Extent (mm)
Epstein[27]	<.10	<3	<50%	<=6		
Epstein[28]	<.15	1		<=6		<3 mm
Irwin[35]		1		<=6		<3 mm
Cupp[36]		1		<=6		<3 mm
Goto[31]	<.10	1		<=6		<2 mm
Epstein[30]	F/T > 0.15	<3	<50%	<=6		
Noguchi[34]	<.15	1		<=6		<3 mm
Augustin[33]	<.10				<1%	
Anast[37]			<10%	<=6		

prolonged an average of 5 years by having prostate cancer death averted.[7] If each prostate cancer death averted adds 5 years to that individual's life, each radical prostatectomy would add 0.6 months of life (60 months per 100 operations), or approximately 3 weeks (unadjusted for quality of life). This is of dubious merit.

Identifying aggressive disease in favorable risk patients

Egawa et al examined PSADT before radical prostatectomy and found that a doubling time of ≤3 years was more common with pT3 disease at radical prostatectomy.[39] McLaren and coauthors also examined PSADT in a watchful-waiting cohort and found that a PSADT of <3 years was associated with clinical progression (defined as palpable enlargement in the tumor nodule or increase in T stage) in over 80% of patients by 18 months from diagnosis. [40] D'Amico and colleagues reported that a rise in PSA of >2 ng/ml/year prior to surgery identified a group of patients who had a 15% prostate cancer mortality rate at 7 years.[41] No patients with a PSA rise of <2.0 ng/ml/year prior to surgery died of the disease. Clearly, therefore, a rise in PSA of >2.0 ng/ml/year, which corresponds to a PSA doubling time (PSADT) of about 3 years or less in a patient with a PSA of 6 ng/ml, identifies a group at risk. The primary concern with using PSADT as a trigger for curative intervention is that it may act as a marker of aggressive disease that has already progressed and is no longer localized. Importantly, 20% of the favorable risk patients had a PSA velocity >2.0 ng/ml/year. Seven percent of these died at 10 years. Thus only 1.4% of the favorable risk cohort died of prostate cancer. If one assumes that the 44% reduction in prostate cancer mortality in the Swedish trial also applies to this group, that means that had these patients been managed with watchful waiting instead of surgery, 2.5% would have died of prostate cancer. Thus the benefit of surgery in favorable risk patients can be estimated at (2.5-1.4)= 1.1%. This translates into a NNT of 91, remarkably close to the NNT analysis above.

Active surveillance

Because the prediction of clinically insignificant disease is problematic and inaccurate, an alternative strategy has been developed that allows patient entry into an expectant management protocol with rigorous monitoring and the option of curative salvage therapy, should signs of progression develop. This is referred to as active surveillance.[18-19]

Choo and Klotz were the first to report on a prospective active surveillance protocol incorporating selective delayed intervention for the subset with rapid PSA progression or grade progression on repeat biopsy.[42-43] The eligibility criteria for this included patients with T1c or T2a prostate cancer, who had Gleason ≤6 and PSA ≤10. For patients over age 70, these were relaxed to include Gleason ≤7 (3+4) and/or PSA ≤15. The current cohort comprises 299 patients. Eighty percent of patients fulfilled the criteria for favorable disease (PSA <10 ng/ml, Gleason score ≤6, stage ≤T2a). The median age was 70 years with an age range of 49 to 84 years. Eighty percent of patients had a Gleason score of 6 or less, and the same proportion had a PSA <10 ng/ml (median 6.5 ng/ml). With a median follow-up of 72 months, 101 patients (34%) came off active surveillance, while 198 have remained on surveillance. Patients came off surveillance for a variety of reasons; in 15% this was because of a rapid biochemical progression, 3% had clinical progression, 4% had histologic progression, and 12% elected treatment based on patient preference only. At 8 years, overall survival was 85% and disease-specific survival was 99%. Only 2 out of 299 patients had died of prostate cancer at the time of writing this review. Both of these patients had a PSADT of <2 years and both deaths occurred 5 years after diagnosis. This suggests that these patients had occult metastases at the time of diagnosis, and their outcome would not have been altered by earlier treatment.

The median PSADT, calculated by logarithmic regression, was 7 years. Twenty two percent of patients had a PSADT of <3 years; 42% had a PSADT of over 10 years, suggesting an indolent course of disease in these patients.

Patients were offered a rebiopsy 1.5–2 years after being placed on the surveillance protocol, and then at 3 year intervals. Of the 243 patients who have been on surveillance for more than 2 years, approximately 75% of patients accepted rebiopsy. A standard 10 core technique was used in most patients. Gleason score remained stable in 92% of patients; 8% demonstrated a significant rise in Gleason score, classed as in increase of ≥2. It is not known whether this represents true grade progression or initial undersampling; however, it is consistent with other similar series, demonstrating a 4% rate of grade progression over 2–3 years.[46]

From this group, 24 patients (8% of the cohort) had a radical prostatectomy for a PSADT of <2 years; all had a Gleason score of 5–6, PSA <10 ng/ml, and tumor

stage pT1–2 at study entry. The final pathology was stage pT2 in 10 patients (42%), pT3a–c in 14 (58%), and N1 in 2 patients (8%). For a group of patients with favorable clinical characteristics, this is a high rate of locally advanced disease.

Discussion

As PSA screening becomes established the initial rise in incidence, referred to as the 'incidence bump', is returning to a new baseline. The initial increased incidence may have included a number of significant cancers diagnosed earlier due to the added lead-time effect of PSA sampling, as well as many insignificant cancers. This new era of post-incidence bump PSA initiated diagnosis, coupled with more extensive biopsy strategies, will result in insignificant cancers comprising a larger proportion of all the prostate cancers diagnosed. This is strongly supported by Stamey et al,[44] who demonstrated that the correlation between the largest prostate cancer volume and PSA has fallen from 0.68 at the beginning of the PSA era, to 0.12 at the present time.

The relatively high proportion of pT3 disease seen in the patients who had a radical prostatectomy for a PSA DT <2 years in this cohort supports the view that a short PSADT is associated with an aggressive tumor cell phenotype. A PSADT of less than 2 years, in patients with otherwise favorable clinical features, portends a high likelihood of developing locally advanced disease. This also suggests that, insofar as curing patients with early rapid biochemical progression is a goal, the optimal PSADT threshold for intervention should be around 3 years. In this series patients with a PSA DT of 3 years or less constituted 22% of the cohort. This cutpoint for intervention remains empirical and speculative. However, the 20%-25% of patients a 3 year doubling time identifies represents a rough approximation of the proportion of good risk patients 'at risk' for disease progression. For patients with a PSA in the 6-10 range, it also approximates an annual rise of 2 ng/ml, an adverse predictor of outcome as described by D'Amico.

The psychological effects of living for many years with untreated cancer are unknown. A companion study to the Holmberg randomized trial of surgery versus watchful waiting in Sweden found no significant psychological difference at 5 years (in worry, anxiety, or depression) between the 2 arms.[45] Surveillance is clearly stressful for some men. However, patients with prostate cancer, whether treated or not, are often concerned about the risk of progression. Concern about PSA recurrence is common amongst both treated and untreated patients. Patients who are educated to appreciate the very indolent natural history of most good risk prostate cancers may avoid much of this anxiety. Further QOL studies focused on this issue are clearly warranted.

A follow up strategy for managing patients with active surveillance and selective delayed intervention is described in Table 3.

Current plans

While the approach of active surveillance with selective delayed intervention makes a great deal of

TABLE 3. **Active surveillance: suggested algorithm for eligibility and follow up**

Eligibility:
PSA ≤10
Gleason ≤6
T1c-T2a
Depending on age and co-morbidity: <3 cores involved, <50% of any one core

Follow up schedule:
PSA, DRE q 3 months x 2 years, then q 6 months assuming PSA is stable
10-12 core biopsy at 1 year, and then every 3 years until age 80
Optional: TRUS on alternate visits

Intervention: For PSA doubling time <3 years (in most cases, based on at least 8 determinations) (about 20% of patients)
For Grade progression to Gleason 7 (4+3) or higher (about 5% of patients)

These are guidelines, and should be modified according to patient age and co-morbidity

sense to many practitioners, it requires validation in a comparative trial. To this end, clinicians in Canada, the United States, England, and Europe have collaborated to initiate a large scale trial comparing the approach described in this article to standard therapy (patient's choice of surgery, brachytherapy, or external beam irradiation) for patients with favorable risk prostate cancer. This study, called the 'START Trial', is due to open in mid-2006 as an intergroup trial. It will likely be supported by the Clinical Trials Support Unit (CTSU) of the NCI. This means that a physician belonging to any cooperative group in the United States or Canada can participate in the trial. We encourage patients and physicians to support this important trial.

Conclusion

Watchful waiting, with palliative intent only, is clearly appropriate for patients who are elderly, have significant comorbidity, and have favorable clinical parameters. The use of comorbidity 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 favorable-risk, young, healthy patients fall into an intermediate zone where there may be benefits of curative treatment, particularly if they have more biologically aggressive disease than suspected by their favorable clinical parameters. In these patients, a policy of close monitoring with selective intervention for those whose cancers 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 long-term surveillance. If patients are selected properly (i.e. good risk and low volume disease) and followed carefully, with early intervention for evidence of progression, it is likely that the majority of men with indolent disease will not suffer from clinical disease progression or prostate cancer death, and the minority with aggressive disease will still be amenable to cure. Using two different approaches, we estimate that the number-needed-to-treat, if all such patients were offered radical prostatectomy compared to the strategy described above is approximately 100 for each patient who avoids a prostate cancer death. Thus, the proportion of patients who die of disease is not likely to be significantly different from the proportion dying in spite of aggressive treatment of all good risk patients at the time of diagnosis. This approach is currently being evaluated in a large scale phase 3 study. □

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