Canary Prostate Active Surveillance Study: Design of a Multi-institutional Active Surveillance Cohort and Biorepository

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Active surveillance is a management plan for localized prostate cancer that offers selective delayed intervention on indication of disease progression, allowing patients to delay or avoid treatment and associated side-effects. Outcomes from centers that promote active surveillance are favorable, with high rates of disease-specific survival. However, there remains a need for prognostic variables or biomarkers that distinguish with high specificity the aggressive cancers that progress on surveillance from the indolent cancers. The Canary Prostate Active Surveillance Study is a multicenter study and a biorepository that will discover and confirm biomarkers of aggressive disease as defined by histologic, prostate-specific antigen, or clinical criteria. UROLOGY 75: 407–413, 2010. © 2010 Elsevier Inc.
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Prostate cancer is a heterogeneous disease. Although various clinical and pathologic parameters are associated with prostate cancer progression and recurrence, the natural history of localized prostate cancer is not completely understood. Prostate cancer is the most commonly diagnosed cancer among men in the United States, and the second leading cause of cancer mortality,[1] although there is clear evidence that a significant percentage of prostate cancers existing in the population will never become clinically evident or cause mortality. Autopsy studies have demonstrated that approximately 1 in 3 men aged > 50 years has histologic evidence of prostate cancer, but up to 80% of the tumors are small in size (< 0.5 cm) and low in grade, suggesting they are clinically insignificant.[2] Furthermore, comparisons of autopsy-detected prostate cancer rates before and after prostate-specific antigen (PSA) testing was introduced, showing a decrease in prevalence after PSA testing became widely used.[3] These data are concordant with studies comparing prostate cancer mortality in the absence and presence of PSA screening, which suggest widespread use of PSA screening may be at least in part

responsible for the decrease in mortality because of prostate cancer from 1990 to 2004.[4-6] However, not only is there is a growing appreciation that widespread PSA screening also results in overdiagnosis of a substantial portion of prostate cancers,[6-8] but also, there is some recent evidence that death rates, albeit very low, do not differ significantly in nonscreened vs screened populations.[9] These controversies underlie the critical need for better predictive tools or biomarkers that will aid clinicians in the discrimination of tumors that warrant treatment and those that fall into the category of overdiagnosis.

RATIONALE FOR ACTIVE SURVEILLANCE

Optimal management of newly diagnosed, clinically localized prostate cancers remains controversial. Therapy options include various forms of radiation or surgery with curative intent, surveillance with or without delayed intervention, systemic therapy, most commonly androgen deprivation, or newly emerging focal ablative therapies. Surgery and radiation, while potentially highly curative in selected patients, are associated with various well established and significant side effects such as incontinence, erectile dysfunction, bowel dysfunction, and lower urinary tract symptoms. Active surveillance is a disease management method that offers selective delayed radical intervention on indication of disease progression as defined by the rate of rise of PSA and/or results of repeat prostate biopsy. This approach began to be used as a management plan in selected patients with clinically localized prostate cancer in the early to mid 1990s.[10] It built upon watchful waiting, which has long been recognized as an approach to manage some cancers, and has been demonstrated to have excellent long-term results in

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selected patients.[11] Active surveillance, which is sometimes called "expectant management with curative intent" differs from the more conventional method of "watchful waiting," a policy of comparatively lax observation using palliative treatment for symptomatic progression.[12] The aim of active surveillance is to identify patients for curative treatment at the first sign of subclinical progression, long before any symptoms or overt signs of tumor progression are evident.

The challenge of managing localized prostate cancer is in distinguishing the patients with clinically relevant cancers, who may benefit from immediate radical intervention, from the remainder who do not need intervention. Several variables, including PSA level and kinetics, biopsy primary and secondary Gleason score, extent of disease on biopsy, and clinical T-stage, are associated with risk of disease progression and metastasis.[13,14] Although there is debate regarding the appropriate PSA threshold for screening, most investigators agree that PSA > 10 ng/mL usually predicts more aggressive tumors.[15] Gleason score is also an independent prognostic variable that influences the outcome of prostate cancer patients,[16] and Gleason sum of 6 or lower is often used to define low-risk prostate cancer.[17] However, analyses of prognostic features of men who have died of prostate cancer indicate that one-third to one-half of men who die from prostate cancer were diagnosed with Gleason 6 grade or lower.[11,18] None of the prognostic variables, alone or together,[19,20] provide sufficient specificity for identifying aggressive disease, and currently over 90% of patients with newly diagnosed prostate cancer are treated.[21,22] These data demonstrate the need for biomarkers for prostate cancer that complement conventional risk assessment. There is a clear need for markers that can predict prostate cancer behavior and that can segregate, with a high degree of specificity, diseases that may be cured with treatment from those that are indolent and for which immediate treatment is unnecessary.

RESULTS OF ACTIVE SURVEILLANCE

Reported outcomes from many centers that promote active surveillance to manage prostate cancer are quite favorable. Presently, there is no consensus on the optimal active surveillance protocol, and the eligibility and treatment criteria, reviewed by van As and Parker[23] and Dall'Era et al,[17] respectively, differ among the various centers. However, all criteria, given in Table 1, resemble those in the report on active surveillance from Toronto, the study with the longest follow-up.[10,25] This study included 299 participants with T1/T2a disease, Gleason score less than or equal to 3 + 4, and PSA < 15 ng/mL. Patients were monitored with digital rectal examination (DRE) and PSA assays every 3 months for 2 years, and then every 6 months if the PSA level was stable. Repeat biopsies with 10-12 cores were repeated at 1 year, and then every 3 years. Patients were free to choose radical treatment at any time, and radical treatment was recommended if the PSA doubling time was < 3 years or if the repeat biopsies showed an upgrading to Gleason 4 + 3 or higher. With a median follow-up of 5 years, 198 participants remained on surveillance and 101 patients (34%) had interventions. Of the 2 participants who died of prostate cancer in the Toronto group, both had a PSA doubling time < 2 years, both were treated radically within 6 months, and developed metastatic disease within a year. Perhaps both of these patients had occult metastatic disease at diagnosis and would not have benefited from immediate radical treatment.[25]

Results from other studies are concordant, as summarized in Table 1. In these reports, about one-third of men on active surveillance received treatment, with high disease-specific survival in all groups. Retrospective analysis of data from participants in the European Randomized Study of Screening for Prostate Cancer who were managed expectantly, both by active surveillance and watchful waiting, and who conformed to active surveillance criteria similar to those used in the initial description of active surveillance,[10] are consistent with results presented in Table 1.[28] Data from 616 men with a median follow-up of 47 months indicated a calculated prostate cancer-specific survival of 100%, which sharply contrasted with the 77% overall survival. These studies, as a whole, demonstrate that an active surveillance strategy using selective delayed intervention for men with low-risk prostate cancer is feasible and is associated with low rates of significant prostate cancer progression and death. However, given the often prolonged natural history of prostate cancer, the median follow-up from these published series remains relatively short. Until there is longer-term data or validation of appropriate surrogate endpoints, results from these studies must be interpreted with caution.

RANDOMIZED TRIALS OF ACTIVE SURVEILLANCE

To truly confirm and validate active surveillance as a management plan for clinically localized prostate cancer, we must wait for the results from large randomized trials comparing active surveillance with active treatment. The Scandinavian Prostate Cancer Group-4 Randomized Trial that randomized 695 men with localized disease between radical prostatectomy and watchful waiting is the only completed randomized trial,[29] although it is important to emphasize that this trial utilized watchful waiting as opposed to active surveillance. At a median follow-up of both 10.8 and 12 years, random assignment to radical prostatectomy was associated with a benefit both in terms of disease-specific mortality and overall survival. Disease-specific mortality at 12 years was 12.5% for the surgery group and 17.9% for the watchful waiting group (hazard ratio 0.65, 95% confidence interval = 0.45-0.94, P = .03). However, the outcome data from this trial were based largely on clinically detected disease and cannot be applied to screen-detected prostate cancer.

Table 1. Select active surveillance cohorts

Study	No. Participants	Median Follow-Up (mo)	Eligibility Criteria	Progression and/or Treatment Criteria	No. Treated (%)	Disease-Specific Survival (%)	No. of Metastatic Disease	Overall Survival
UCSF[24]	321	43	PSA < 10 ng/mL Gleason sum ≤ 6 (no pattern 4 and 5) < 33% Cores involved Clinical T1/T2a	Rising PSA (PSAV > 0.75 ng/mL/y) Gleason sum ≥ 7 on rebiopsy Increase in volume by biopsy parameters	24	100	None identified	100%
Toronto[10,25]	299	64	PSA ≤ 10 ng/mL (≤ 15 ng/mL if aged > 70 years) Gleason sum ≤ 6 [≤ 7 (3 + 4) if aged > 70 years] Clinical T1c-T2a	PSADT ≤ 3 y Gleason sum ≥ 7 on rebiopsy DRE change	34	99.3 After 8 y	2 (Resulted in 2 deaths)	85%
Johns Hopkins[26]	407	41	PSA density ≤ 0.15 ng/mL/cm^3 Gleason sum ≤ 6 (no pattern 4 and 5) ≤ 2 Cores involved ≤ 50% Any 1 core involved Clinical T1c	Gleason sum ≥ 7 on rebiopsy (any pattern 4 or 5) > 2 Cores involved > 50% Of any 1 core involved	25	100	None reported	98%
MSK and Baylor[27]	88	44	Gleason sum ≤ 7 Clinical T1-2	Score based on: Gleason score increase PSA velocity > 0.75 ng/mL/y Increase DRE/TRUS detected lesion Increase biopsy volume	35	Not reported	Not reported	Not reported
Royal Marsden Hospital[23]	326	22	PSA ≤ 15 ng/mL Gleason sum ≤ 7 (3 + 4) < 50% cores involved < 10 mm Any 1 core Clinical T1/T2a Life expectancy > 10 y	PSA velocity > 1 ng/mL/y Gleason score ≥ 4 + 3 on repeat biopsy > 50% Core involved	20	100	0	98%

Only 5% of prostate cancers, for example, were detected by PSA testing, and three-quarters of enrollees had cT2 tumors with extracapsular extension noted in about 50%, which is a substantially greater tumor volume than noted in populations enrolled in active surveillance studies in the United States and Canada. Accordingly, it is interesting to compare the 10-year disease-specific mortality of 14% in watchful waiting arm of the Scandinavian trial to the 8-year disease-specific mortality of 1% in the Toronto active surveillance experience, discussed earlier.

There are currently 3 other randomized trials that aim to compare active treatment with expectant management of prostate cancer. The Prostate Cancer Intervention vs Observation Trial, for which enrollment has been completed with 731 participants, also compares radical prostatectomy with watchful waiting.[30] An ethnically diverse group of patients with cancers detected through PSA-screening were enrolled. However, if radical treatment for all (eg, prostatectomy) turns out to be better than radical treatment for none (eg, observation), it will beg the question of whether treatment for a select group based on progression on active surveillance would be as effective but less morbid with similar disease-specific mortality. The Prostate Testing for Cancer and Treatment compares radical prostatectomy, external beam radiotherapy, and active monitoring.[31] The study aims to enroll 2000 men, and allows active therapy for a small subset of men with very rapid PSA doubling time.

The Phase III Study of Active Surveillance Therapy against Radical Treatment in Patients Diagnosed with Favorable Risk Prostate Cancer will compare disease-specific survival of patients with favorable risk prostate cancer who have been randomly assigned, at the time of initial diagnosis, to radical treatment or active surveillance. This trial, which opened for accrual in 2007, is the only randomized trial with an active surveillance protocol in which participants will be offered treatment based on prespecified biochemical, histologic, or clinical criteria. Those receiving treatment, either immediately or upon disease progression, will have a choice between prostatectomy or radiotherapy.[32] Results of this study should provide valuable information about whether active surveillance is superior, equal, or inferior to active treatment for the management of select clinically localized prostate cancer.

ACTIVE SURVEILLANCE AND BIOMARKERS OF AGGRESSIVE DISEASE

Active surveillance provides the opportunity, if biospecimens are collected, to evaluate candidate biomarkers that could be used to target treatment to men who stand to benefit from therapy, and avoid intervention in those for whom it is unnecessary. For example, fusion products of the androgen-regulated *TMPRSS2* gene and *ETS* transcription factor genes, which have been identified as a common translocation in a majority of prostate cancers,[33] have been associated with higher risk disease features in

Table 2. Summary of PASS entry and progression criteria

Eligibility
  Clinical stage T1–2, NX/0, MX/0.
  No previous treatment for prostate cancer (including hormonal therapy*, radiation therapy, surgery, or chemotherapy).
  ECOG performance status 0 or 1.
  Elected active surveillance as preferred management plan for prostate cancer.
  If diagnosis ≤ 1 year of entry, at least 1 biopsy with ≥ 10 cores.
  If diagnosis > 1 year before entry, minimum of 2 biopsies, 1 ≤ 2 years before entry.
  No other malignancies except adequately treated nonmelanoma skin cancer or superficial bladder cancer, or solid tumors curatively treated with no evidence of disease for > 5 years.
Progression
  PSA doubling time < 3 years.
  Any increase in Gleason grade.
  Clinical progression.

* Hormonal therapy includes luteinizing hormone releasing hormone (LHRH) agonists and antiandrogens, but not 5-α reductase inhibitors or testosterone.

small cohorts.[34,35] However, the *TMPRSS2-ERG* gene fusion is not always associated with outcome,[36] and further studies in the prostate tissue or urine of controlled cohorts are necessary to determine the prognostic value of the fusion products. Of the active surveillance studies currently being conducted, we are aware of only 2 that collect blood, urine, and tissue that may be used for biomarker studies—the study at Royal Marsden Hospital in the United Kingdom[12,23] and the Canary Prostate Active Surveillance Study, described later in the text.

CANARY PROSTATE ACTIVE SURVEILLANCE STUDY AND BIOREPOSITORY

The Canary Prostate Active Surveillance Study (PASS) is a multicenter, prospective active surveillance study that is currently enrolling participants at Stanford University, University of California, San Francisco, University of British Columbia, University of Washington, and University of Texas Health Science Center at San Antonio. The study is supported by both the Canary Foundation and the Early Detection Research Network (EDRN) of the National Cancer Institute. The primary objective is to discover and confirm biomarkers that predict aggressive disease as defined by prespecified histologic, PSA, and clinical criteria, or outcomes based on those variables. Secondary objectives are to determine the proportion of patients on active surveillance who progress based on defined criteria, and to determine the clinical predictors of disease progression. The study is recruiting patients with previously untreated, early stage prostate cancer, regardless of date of diagnosis, who have chosen active surveillance as a preferred management plan for prostate cancer. The eligibility criteria are given

Table 3. Patient evaluation timeline

Month	Entry	3	6	9	12	15	18	21	24	27	//	Tx.
Measure												
PSA	x	x	x	x	x	x	x	x	x	x		
Blood	x		x		x		x		x			x
DRE	x		x		x		x		x			
Urine (post DRE)	x		x		x		x		x			x
Tissue/Bx: diagnosed ≤ 1 y	x*			x†					x			x
Tissue/Bx: diagnosed > 1 y	x‡								x			
DNA (from WBC)	x											

* If no biopsy with at least 10 cores.
† Biopsy performed at 6-12 months from the time of entry.
‡ If only 1 existing biopsy or if most recent biopsy > 2 years before entry and number of previous biopsies ≥ 2; if biopsy not performed at enrollment, a study biopsy will be conducted 2 years from the most recent biopsy, rounded to nearest 3-month study visit.

in Table 2. These criteria are deliberately broad and are designed to allow most men who choose active surveillance without confounding conditions to enroll. The broad scope of disease characteristics is likely to provide greater insight into the natural history of prostate cancer and serve as the basis for a rich biospecimen resource.

Participants will be evaluated by serial DRE, serum PSA, and prostate biopsies according to the timeline outlined in Table 3. Serum PSA measurements are performed every 3 months from the time of entry, and physical examinations are performed at study entry and every 6 months from the time of enrollment. Patients who are diagnosed within 1 year before study entry will undergo repeat biopsy at the baseline visit if a biopsy with at least 10 cores is not available, at 6-12 months from the baseline visit, at 2 years, then every 2 years. Patients who are diagnosed at > 1 year before the baseline visit will undergo repeat biopsy with the following schedule: at baseline visit if only 1 prior biopsy or if the most recent biopsy was > 2 years before the baseline visit, and then every 2 years from the most recent biopsy. The rationale for this schema is to ensure that initial diagnostic biopsy adequately samples the prostate, to avoid false-negative diagnosis of high-grade cancer, and to capture early histologic progression. Patients are free to choose treatment at any time. Progression in PASS will be defined when patients fulfill one or more of the criteria summarized in Table 2. Biochemical progression is defined as a PSA doubling time of < 3 years, based on at least 5 separate consecutive measurements over a minimum of 12 months and maximum of 24 months. PSA values from the time of diagnosis will be used in calculations. Histologic/Grade progression is any increase in tumor grade. Grade progression will be calculated from the highest existing Gleason grade. Clinical progression can either be local, defined as a stepwise increase in tumor stage by DRE or identification of regional or distant metastasis, as defined by radiology, cytology, or histology at sites remote from the prostate. Progression events will be noted by local investigators, programmed in the study database, and adjudicated by the PASS Endpoints Committee. These definitions of disease progression are sensitive but not necessarily specific for disease progression. Therefore, although active treatment will be offered to a participant should any of these elements be met, the participant may opt to remain on active surveillance. If this occurs, a new PSA/stage/grade status will be assigned and further progression events will be determined using the new baseline criteria.

A paramount objective of PASS is the formation of a biospecimen repository with associated clinical data that will serve as a rich resource for biomarker and prediction studies. Blood and urine are collected at baseline, every subsequent 6 months, and, if applicable, at the time of intervention; blood is also collected at baseline for isolation of both DNA and white blood cells for future immortalization (Table 3). Frozen cores from needle core biopsies are collected, and, if a participant undergoes a radical prostatectomy, both formalin-fixed paraffin embedded and fresh frozen tissue are collected. Specimens are collected and processed according to uniform standard operating procedures at all institutions. Close adherence to standard operating procedures is maintained by in-person staff training for specimen processing and data collection before initiation of the study as well as regular site visits and inspection of specimens. Data collected at baseline and every subsequent 6 months include demographics (eg, age, race and ethnicity, height and weight, cigarette and alcohol use, family history of prostate cancer), medication use, and clinical data (eg, PSA, prostate biopsy, and cancer history) while on the study and from the 5 years before enrollment. In addition, information on diet and supplement use is collected at baseline using validated instruments, and changes in supplement use are followed yearly. Study coordination and data management are conducted by the Data Management and Coordinating Center (DMCC) of the EDRN. Deidentified data are stored in the Validation Studies Information Management System,[37] a secure database managed by the DMCC, and location and attributes of all specimens are tracked in Validation Studies Information Management System. Specimens are stored in a PASS central biorepository. Proposals from the scientific community to use PASS specimens to interrogate biomarkers will be reviewed by the PASS Biomarker Review Committee.

The primary objective for developing the PASS repository is to discover and/or confirm biomarkers that are

predictive of progressive and/or aggressive prostate cancer, with an emphasis on confirmation. The sample size and power are therefore based on confirmation of a biomarker after its initial discovery. A desirable biomarker should have high specificity to identify the subset of patients at high risk for progression while minimizing the proportion of men for whom aggressive treatment is undertaken. Therefore, the sensitivity of a biomarker is evaluated at 95% specificity. The threshold of a biomarker corresponding to 95% specificity does not have to be prefixed before the confirmation study, and it can be estimated from PASS study data within the confirmation study. The proportion of disease progression at 3 and 5 years from diagnosis is estimated at 25% and 33%. At 95% specificity, a power of 90% is desired to confirm a sensitivity > 10% (which is unacceptable) if the true sensitivity is 30% or better. Point estimates of sensitivity, specificity, and threshold as well as their 95% confidence intervals will be calculated. The samples size also depends on the slope of receiver operating characteristic curve at 95% specificity, usually quite steep when specificity is near 100%. For PASS power analysis, a slope parameter of 4 was used.[38] On the basis of these assumptions, for a cohort with at least 5-year follow up, this study requires 125 men with progression and 250 men without progression, for a total of 375 participants, or 1875 total person years of follow-up. The intent of PASS is to enroll at least 400 participants.

CONCLUSIONS

Active surveillance currently offers a management plan for early stage, low-grade prostate cancer that allows patients at minimum to defer, and possibly to completely avoid, treatment and the attendant complications of such treatment. The ability to target treatment to those who will benefit from it is still imperfect. An alternative approach to the management of men with potentially low-risk prostate cancers would be to use markers of disease risk at the time of diagnosis and thereby segregate those who would potentially benefit from treatment from those for whom treatment is unnecessary. Active surveillance studies such as PASS provide the opportunity to study the natural history of localized prostate cancer and to evaluate candidate biomarkers. Ultimately, with the validation of these markers, tens of thousands of men in the United States alone could be spared the cost and morbidity associated with the treatment of prostate cancer.

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