Title
Active surveillance for the management of prostate cancer in a contemporary cohort.

Journal
Cancer, 112(12)

ISSN
0008-543X

Authors
Dall'Era, Marc A
Konety, Badrinath R
Cowan, Janet E
et al.

Publication Date
2008-06-01

DOI
10.1002/cncr.23502

Peer reviewed

Active Surveillance for the Management of Prostate Cancer in a Contemporary Cohort

Marc A. Dall'Era, MD[1]
Badrinath R. Konety, MD[1]
Janet E. Cowan, MA[1]
Katsuto Shinohara, MD[1]
Frank Stauf[1]
Matthew R. Cooperberg, MD[1]
Maxwell V. Meng, MD[1]
Christopher J. Kane, MD[1]
Nanette Perez, RN, NP[1]
Viraj A. Master, MD[2]
Peter R. Carroll, MD[1]

[1] Department of Urology and the Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, San Francisco, California.

[2] Department of Urology, Emory University, Atlanta, Georgia.

See editorial on pages 2631–4, this issue.

Supported by National Institutes of Health Prostate Cancer Specialized Programs of Research Excellence (SPORE) grant 1P50CA089520-01.

Address for reprints: Marc A Dall'Era, MD, Department of Urology, University of California at San Francisco, 1600 Divisadero, Box 1695, San Francisco, CA 94143-1695; Fax: (415) 353-7093; E-mail: mdallera@urology.ucsf.edu

Received September 4, 2007; revision received December 21, 2007; accepted January 2, 2008.

BACKGROUND. Active surveillance followed by selective treatment for men who have evidence of disease progression may be an option for select patients with early-stage prostate cancer. In this article, the authors report their experience in a contemporary cohort of men with prostate cancer who were managed with active surveillance.

METHODS. All men who were managed initially with active surveillance were identified through the authors' institutional database. Selection criteria for active surveillance included: prostate-specific antigen (PSA) <10 ng/mL, biopsy Gleason sum ≤6 with no pattern 4 or 5, cancer involvement of <33% of biopsy cores, and clinical stage T1/T2a tumor. Patients were followed with PSA measurements and digital rectal examination every 3 to 6 months and with transrectal ultrasound at 6- to 12-month intervals. Beginning in 2003, patients also underwent repeat prostate biopsy at 12 to 24 months. The primary outcome measured was active treatment. Evidence of disease progression, defined as an increase in rebiopsy Gleason sum or significant PSA velocity changes (>0.75 ng/mL per year), was a secondary outcome. Chi-square and log-rank tests were used to compare groups. The association between clinical characteristics and receipt of active treatment was analyzed by using Cox proportional hazards regression.

RESULTS. Three hundred twenty-one men (mean age [±standard deviation]: 63.4 ± 8.5 years) selected active surveillance as their initial management. The overall median follow-up was 3.6 years (range, 1–17 years). The initial mean PSA level was 6.5 ± 3.9 ng/mL. One hundred twenty men (37%) met at least 1 criterion for progression. Overall, 38% of men had higher grade on repeat biopsy, and 26% of men had a PSA velocity >0.75 ng/mL per year. Seventy-eight men (24%) received secondary treatment at a median 3 years (range, 1–17 years) after diagnosis. Approximately 13% of patients with no disease progression elected to obtain treatment. PSA density at diagnosis and rise in Gleason score on repeat biopsy were associated significantly with receipt of secondary treatment. The disease-specific survival rate was 100%.

CONCLUSIONS. Selected individuals with early-stage prostate cancer may be candidates for active surveillance. Specific criteria can be and need to be developed to select the most appropriate individuals for this form of management and to monitor disease progression. A small attrition rate can be expected because of men who are unable or unwilling to tolerate surveillance. ***Cancer*** **2008;112:2664–70.** © *2008 American Cancer Society.*

KEYWORDS: prostate cancer, active surveillance, watchful waiting, criteria.

Prostate cancer demonstrates remarkably heterogeneous behavior. Retrospective studies suggest that untreated, low-grade, localized cancer may represent a limited risk to the patient in terms of symptoms or cancer death.[1,2] In addition, aggressive screening efforts have resulted in the detection of many early-stage lesions,

DOI 10.1002/cncr.23502
Published online 23 April 2008 in Wiley InterScience (www.interscience.wiley.com).

which have uncertain biologic and clinical significance.[3] Data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry indicate that the proportion of patients with newly diagnosed prostate cancer who had low-risk disease increased from 29.8% during 1989 through 1992 to 45.3% during 1999 through 2001.[4,5] Despite such stage migration, active treatment rather than surveillance is more common today. The use of androgen-deprivation therapy as monotherapy or brachytherapy has increased 3-fold, whereas the use of watchful waiting or active surveillance has decreased by 2-fold.[6,7] It is unclear whether this is because of patient preferences, physician guidance, or a combination of both.

By using the power of risk-stratification schemas to better identify cancers with a low risk of progression, attempts are being made to devise alternative management approaches. The strategy of active surveillance with delayed curative therapy has been explored by a few centers.[8-10] Variables associated with progression have included prostate-specific antigen (PSA) kinetics, increasing Gleason grade, and the clinical development of metastases (bone pain, ureteral obstruction, and bladder outlet obstruction). We have instituted an active surveillance program at our institution that enrolls patients prospectively. This is a report of our experience with active surveillance and deferred therapy for the management of early-stage prostate cancer.

MATERIALS AND METHODS

Patients who were enrolled prospectively into an institutional active surveillance program after a diagnosis of prostate cancer were identified through the University of California at San Francisco Urologic Oncology Database, which contains >450 data elements per patient. Inclusion criteria include no therapy received before diagnosis/presentation at our institution, primary therapy designated as active surveillance, and no primary treatment (surgery, external beam radiation, brachytherapy, or androgen-ablation therapy) received within 6 months of diagnosis. Patients selectively were offered active surveillance if they met the following diagnostic criteria: PSA <10 ng/mL, Gleason sum ≤6, absence of Gleason grade 4 or 5, cancer involvement of <33% of biopsy cores, and clinical T1/T2a tumor. In addition to these men, some patients who did not meet these criteria were placed on active surveillance for other medical reasons or by personal choice and were analyzed separately. Of all patients in the database, we identified 513 men who were diagnosed after 1991 and who received active surveillance as primary management. Three hundred twenty consecutive men had been on active surveillance for at least 1 year and had sufficient data points for this analysis. The surveillance regimen consisted of office visits with digital rectal examination, serial PSA measurements (usually at 3-month intervals), and transrectal ultrasonography (TRUS) at 6- to 12-month intervals. Starting in 2003, repeat prostate biopsies were recommended at 12- to 24-month intervals for all patients. It is interesting to note that, in addition to periodic physician visits, starting in 2002, a nurse practitioner made regular telephone and e-mail contact with patients to ensure surveillance compliance and to address patient concerns and anxiety.

Active treatment was the primary outcome analyzed as the endpoint for active surveillance. Progression was a secondary outcome measure and was defined as increase in Gleason grade on rebiopsy or increase in PSA velocity (PSAV) of >0.75 ng/mL per year. To make our data more comparable to data from other large series, and because emerging data suggest that other parameters of PSA kinetics may be better for predicting aggressive tumor biology, we also report the proportion of men with PSAV >2 ng/mL per year and a PSA doubling time <2 years.[11–13] Ultrasound data were not included in this study: We determined that the data were inconsistent because of interobserver variability and apparent fluctuations in lesion size.

Types of secondary treatment and the times to progression and to treatment were evaluated. The chi-square test was used for intergroup comparisons. The log-rank test was used to compare the time to secondary treatment between patients with and without disease progression. The product-limit method was used to obtain estimates of freedom from prostate cancer progression. Cox proportional-hazards regression analysis was used to assess the associations of various markers of progression with the likelihood of receiving secondary treatment. All statistical analyses were performed using SAS version 9.1 for Windows (SAS Institute, Cary, NC).

RESULTS

Active surveillance accrual has increased over time, with a relatively low annual enrollment in the early 1990s, to the enrollment of 91 men in the first half of 2007 (Fig. 1), and to >500 men currently enrolled. The mean age (±standard deviation) of patients in the sample cohort of 321 men was 63.4 ± 8.5 years (median, 64 years; range, 40-86 years). The mean PSA level at diagnosis was 6.5 ± 3.9 ng/mL (median,

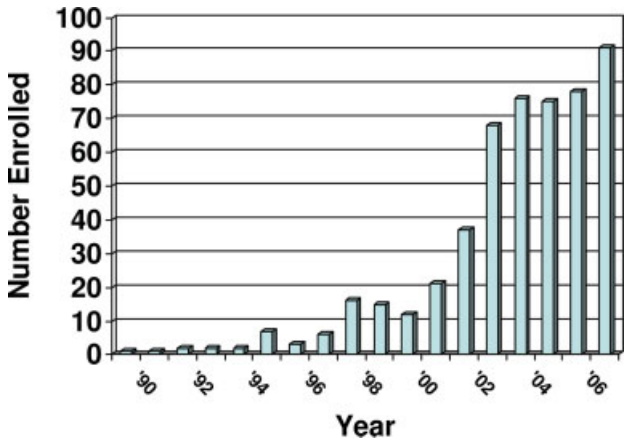

FIGURE 1. Yearly accrual into active surveillance at the University of California at San Francisco.

6 ng/mL; range, 0.3–29.6 ng/mL). The median Gleason score was 6 (range, 5–8), and the mean percent of positive cores was 20.3% ± 20% (median, 14%; range, 3%-100%). Demographic and disease-related baseline data on the cohort are shown in Table 1. Seventy-one percent of patients were stratified as low risk, 26% were stratified as intermediate risk, and 3% were stratified as high risk using the criteria described by D'Amico et al.[14] The median patient follow-up was 3.6 years (range, 1–17 years). One hundred sixty-five men (51%) underwent at least 2 prostate needle biopsies to analyze for grade progression. Three hundred five men (95%) had at least 3 PSA values available for velocity calculations.

With a median time to treatment of 3 years (range, 1–17 years), 78 patients (24% of the cohort) received definitive therapy. Twenty-six men (8%) underwent radical prostatectomy, and 35 men (11%) received radiation therapy without androgen deprivation; whereas 7 men (2%) received radiation with hormone therapy (Table 2). Nine patients (3%) received primary androgen-deprivation therapy. Fifty-two treated men (16% of the cohort) had clinical evidence of disease progression according to the defined criteria, whereas 26 men (8%) were treated because of personal choice in the absence of any clinical evidence of disease progression. Seventy-eight men (26% of the men with sufficient PSA values) had a PSAV >0.75 ng/mL per year, whereas 46 men (15%) had a PSAV >2 ng/mL per year. The median PSA doubling time was 6.7 years. Sixty-three men (38% of the cohort with at least 2 biopsies) experienced a rise in Gleason score on repeat biopsy.

The overall estimated actuarial probabilities of not receiving treatment at 2 years and at 5 years were 85% and 67%, respectively. Figure 2a shows the actuarial probabilities of not receiving treatment stratified according to whether patients were deemed to have progressed on surveillance or not. If we limited the analysis to only men with a minimum of 5 years of follow-up (n = 70 men), then the actuarial freedom from treatment was 93% and 85% for men who did not progress and men who did progress, respectively (Fig. 2b). A series of multivariate Cox proportional-hazards regression models were run that included age at diagnosis, race, relationship status, clinical risk group, PSA density (PSAD), and the 2 clinical markers of progression to examine the ability of these variables to predict treatment. There were no significant baseline differences between patients who received treatment and patients who did not receive treatment in terms of age, race, clinical risk group, initial PSA, percent free PSA, tumor (T) classification, Gleason grade, percent positive biopsy cores, or overall selection criteria for active surveillance. A PSAV >0.75 ng/mL per year was not an independent predictor of treatment in the models analyzed. PSAD at diagnosis ($P = .0002$) and increase in Gleason grade ($P = .0001$) significantly predicted the time to active treatment. Patients who had a

TABLE 1
Demographic and Disease-related Characteristics of Patients in the Cohort

Characteristic	No. of patients (%)		
	All patients	Continued surveillance	Active treatment
Age, y			
<65	171 (53)	135 (56)	36 (46)
≥65	150 (47)	108 (44)	42 (54)
PSA, ng/mL			
≤10	262 (82)	202 (89)	60 (82)
>10	38 (12)	25 (11)	13 (18)
Tumor classification			
T1	198 (62)	152 (64)	46 (59)
T2	119 (38)	87 (36)	32 (41)
Gleason sum			
<7	276 (91)	205 (91)	71 (93)
≥7	26 (9)	21 (9)	5 (7)
% Total cores positive for cancer			
<33	229 (82)	177 (84)	52 (76)
≥33	50 (18)	34 (16)	16 (24)
% Any single core involved with cancer			
<50	318 (99)	240 (99)	78 (100)
≥50	3 (1)	3 (1)	0 (0)
Clinical risk category			
Low	204 (71)	154 (71)	50 (70)
Intermediate	74 (26)	54 (25)	20 (28)
High	9 (3)	8 (4)	1 (1)

PSA indicates prostate-specific antigen.

TABLE 2
Treatment Type Received and Indication for Treatment*

Variable	No. of patients (%)			
	Total no.	Gleason increase	High PSAV (>0.75 ng/mL/y)	Patient choice (ie, no disease progression)
Radical prostatectomy	26	11 (42)	10 (38)	9 (35)
Radiotherapy without androgen deprivation	35	16 (46)	13 (37)	9 (26)
Radiotherapy with androgen deprivation	7	4 (57)	2 (29)	2 (29)
Primary androgen deprivation	9	3 (33%)	2 (22%)	5 (56)

PSAV indicates prostate-specific antigen velocity.
* Several patients had >1 indication. Percentages shown represent a fraction of each treatment group.

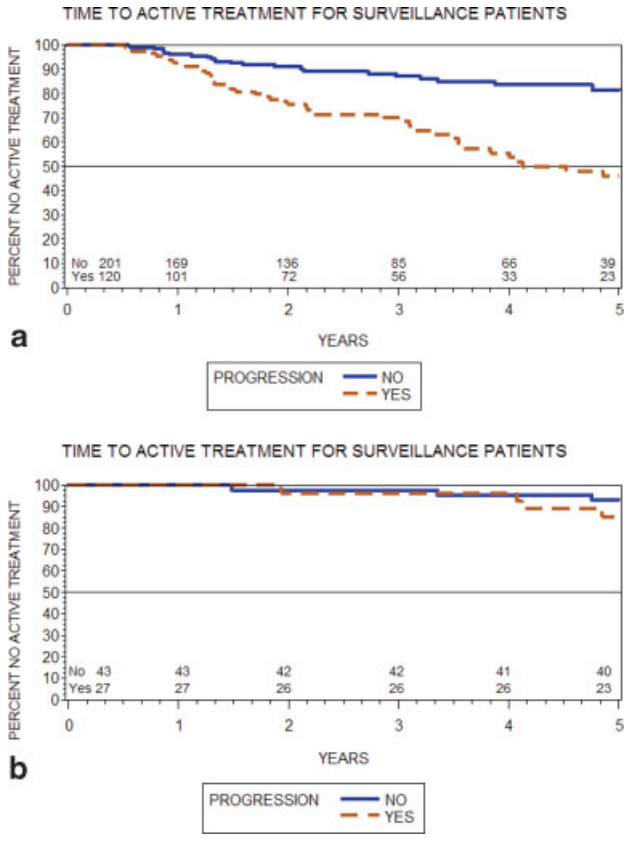

FIGURE 2. (a) Kaplan-Meier estimates of the time to definitive treatment for patients who did and did not develop disease progression (log-rank test; $P \leq .0001$) (b) Kaplan-Meier estimates of the time to definitive treatment for patients who did and did not develop disease progression, limited to men with at least 5 years of follow-up (log-rank test; $P = .04$).

PSAD $\geq$0.15 ng/mL/cm^3 at diagnosis were more likely to receive active treatment (hazard ratio, 5.2; 95% confidence interval, 2.2–12.2) than men who had a lower PSAD. Patients who had an increase in Gleason grade on repeat biopsy were 3.9 times as likely to undergo active treatment as men who had no increase in Gleason grade (hazard ratio, 3.9; 95% confidence interval, 2.0–7.7).

To date, the 5-year disease-specific and overall survival rates in this cohort are both 100%, although the median follow-up is short at 3.6 years, and the 10-year overall survival rate is 98% for 42 evaluable men. No patient has experienced symptomatic evidence of bony or soft tissue metastatic disease, although bone scans were not performed routinely. One patient has experienced biochemical recurrence at 3 years after radical prostatectomy.

DISCUSSION

The treatment of prostate cancer can be associated with significant decrements in quality of life.[15,16] Therefore, watchful waiting, or active surveillance with selective delayed curative therapy, may represent an attractive management option for patients with low-risk disease. Although men on watchful waiting have reported decrements in health-related quality of life domains, such as sexual health, these rates are less than those observed after prostate cancer treatments and are most likely because of age-related declines in function.[17]

Although there is increasing interest in examining active surveillance as a legitimate management approach for low-risk prostate cancer, the criteria for patient selection and definition of progressive disease vary between studies.[8–10,18] In general, most active surveillance studies have restricted patient selection by using Gleason grade and PSA cutoff points; however, specific threshold values vary between studies. Klotz entered patients with Gleason scores $\leq$7, whereas we restricted the candidates to those with Gleason scores $\leq$6.[19] Carter et al. used PSA values $\leq$20 ng/mL, whereas our cohort generally

was limited to men who had PSA values <10 ng/mL.[8] The inclusion of patients with higher Gleason scores and higher PSA values likely groups patients with pure low-risk features and those with intermediate risk features together and may affect progression estimates and treatment outcomes.

An upward migration in biopsy Gleason grade was the most consistent baseline factor associated with the receipt of secondary definitive therapy and occurred in 38% of patients in our cohort. Carter et al. also noted a similar 30% progression by Gleason sum in their series of patients.[8] In contrast, Klotz observed that only 16% of patients had histologic progression.[18] This lower rate of histologic progression in the Toronto cohort most likely is because of expanded entry criteria to include men with Gleason 7 disease. Ninety-one percent of patients in our cohort entered with Gleason 3 + 3 disease, and nearly all grade progression was to Gleason 3 + 4 disease.

A significant proportion of men on active surveillance most likely are upgraded because of sampling error on initial biopsy rather than experiencing pure grade progression given the short time between biopsies. Epstein et al. used serial biopsies over time to demonstrate that dedifferentiation of prostate cancer over this short time is unlikely to occur.[20] The median time to grade progression in our cohort was 34 months (range, 3–127 months). It is well documented that up to 30% of men who undergo radical prostatectomy for presumably Gleason 3 + 3 disease will have components of Gleason 4 or 5 disease on final pathologic analysis.[21] Extended pattern biopsies can reduce the risk of under sampling and grading of prostate cancers.[22] At our institution, we have noted a greater frequency of Gleason upgrading on subsequent in-house biopsy among men who underwent their initial biopsy remotely (26% vs 16% of men who underwent their initial biopsy in-house). This underscores the importance of a well performed, consistent biopsy strategy in properly selecting patients for active surveillance and for following them over time, because significant clinical under grading can occur. Early, confirmatory rebiopsy also may function to reduce patient and physician anxiety regarding surveillance, which, ultimately may prove to be a stronger driver of treatment than evidence of disease progression.[23]

TRUS is used to follow the size of detectable lesions in our protocol. To the best of our knowledge, only 1 study to date has examined the utility of TRUS to gauge progression in a watchful-waiting cohort. Hruby et al. performed TRUS on 28 patients who were part of the watchful-waiting cohort reported by Klotz.[24] Those patients had progressed on the basis of PSA doubling time <2 years or with histologic/clinical progression, and each patient had undergone a median of 3 TRUS studies. Only 7 of 28 patients (25%) had changes on TRUS consistent with progression, and the authors concluded that serial TRUS had limited value as a determinant of disease progression. In that retrospective study, TRUS was performed by at least 5 different clinicians (urologists and radiologists), and only 53% of patients had 2 or more TRUS sessions performed by the same clinician, possibly giving rise to significant interobserver variability. We have observed that it is not uncommon for TRUS-detected lesions to vary between examinations, and what constitutes significant change is unclear.

It has been demonstrated that baseline PSAD is associated with disease progression and adverse pathologic features after prostatectomy in men on active surveillance.[8,25,26] Previous studies have described the association between PSAD, tumor volume, and tumor grade. Epstein et al. reported that a PSAD <0.1 ng/mL/cm^3 in patients with low-grade disease at the time of biopsy predicted features of indolent tumors at final pathology after prostatectomy (defined as tumor <0.2 cm^3 confined to the prostate with Gleason score $\leq$6).[27] Men in our cohort with higher baseline PSAD (>0.15 ng/mL/cm^3) were more likely to undergo treatment than men with lower PSAD independent of grade progression or PSAV. Carter et al. have incorporated PSAD into their inclusion criteria and suggest that men who are considered for surveillance should have a PSAD <0.1 ng/mL/cm^3.[28] It is unclear whether these data reflect simply increased sampling error in larger glands or actual differences in tumor biology. These data do suggest that men with higher densities may not be optimal candidates for surveillance, are at increased risk for progression, and require careful characterization with repeat, high-quality, extended core biopsies early during the surveillance period.

The current series demonstrates a low rate of attrition of 8% from the active surveillance protocol. Other recent series from Toronto and Memorial Sloan-Kettering demonstrated higher attrition rates of 16% and 23%, respectively.[10,18] It is possible that, with longer follow-up, more patients may withdraw from active surveillance because of the burden of uncertainty of living with cancer. In the alternative, the attrition may be caused by the influence of frequent communication with a practitioner intimately involved with the active surveillance program. A small, prospective, randomized trial of 41 patients on a watchful-waiting protocol demonstrated that

patients on the experimental (intervention) arm, who received 5 weekly calls from a nurse, had both an increase in quality of life ($P = .01$) and decreased confusion ($P = .04$) as measured on multiple validated questionnaires.[29]

There are several limitations to the current study. There may be a self-selection bias on the part of these patients who are presenting to a referral center. Progression criteria that were used in the study, and others reported in the literature, are not validated, which is true for many of the progression criteria currently used in active surveillance series. Although we observed a nearly 100% survival rate, longer follow-up clearly will be necessary to determine the impact of this approach on overall survival. Roemeling et al. attempted to validate selection criteria (PSA $\leq$15 ng/mL, Gleason score $\leq$6, 1–2 positive biopsy cores, PSAD $<$0.2 ng/mL/cm^3, and stage T1c/T2 disease) for active surveillance by identifying men who met these criteria and were identified through the European Randomized Study of Screening for Prostate Cancer.[30] Of 293 men who met these criteria, 64 men chose active surveillance; and, at a mean follow-up of 81 months, there were no prostate cancer-related deaths in the management group. None of the prostate cancer-related deaths were in the active surveillance group, and 19 men (30%) chose delayed definitive therapy.

Active surveillance is a feasible option for well selected patients with prostate cancer who have low-risk features. Although disease progression determined by PSA or Gleason grade is observed in approximately 33% of these low-risk patients, secondary treatment is adopted by only a subset of these patients, and the others remain on active surveillance. Gleason grade change is the most important driver for the initiation of secondary treatment in our experience. A small (8%) voluntary attrition rate is observed without evidence of disease progression, suggesting that most men can tolerate the anxiety of living with a prostate cancer diagnosis. This approach may permit us to better select patients with intermediate risk or high-risk disease who may benefit from therapy despite shorter life expectancy.

REFERENCES

1. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. Long-term survival among men with conservatively treated localized prostate cancer. *JAMA*. 1995;274:626–631.
2. Johansson JE, Holmberg L, Johansson S, Bergstrom R, Adami HO. Fifteen-year survival in prostate cancer. A prospective, population-based study in Sweden. *JAMA*. 1997; 277:467–471.
3. Humphrey PA, Keetch DW, Smith DS, Shepherd DL, Catalona WJ. Prospective characterization of pathological features of prostatic carcinomas detected via serum prostate specific antigen based screening. *J Urol*. 1996;155:816–820.
4. Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR. The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol*. 2004;22:2141–2149.
5. Cooperberg MR, Park S, Carroll PR. Prostate cancer 2004: insights from national disease registries. *Oncology (Williston Park)*. 2004;18:1239–1247; discussion 1248-1250, 1256-1258.
6. Cooperberg MR, Broering JM, Litwin MS, et al. The contemporary management of prostate cancer in the United States: lessons from the Cancer of the Prostate Strategic Urologic Research Endeavor (CapSURE), a national disease registry. *J Urol*. 2004;171:1393–1401.
7. Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR. National practice patterns and time trends in androgen ablation for localized prostate cancer. *J Natl Cancer Inst*. 2003;95:981–989.
8. Carter HB, Walsh PC, Landis P, Epstein JI. Expectant management of nonpalpable prostate cancer with curative intent: preliminary results. *J Urol*. 2002;167:1231–1234.
9. Carter CA, Donahue T, Sun L, et al. Temporarily deferred therapy (watchful waiting) for men younger than 70 years and with low-risk localized prostate cancer in the prostate-specific antigen era. *J Clin Oncol*. 2003;21:4001–4008.
10. Patel MI, DeConcini DT, Lopez-Corona E, Ohori M, Wheeler T, Scardino PT. An analysis of men with clinically localized prostate cancer who deferred definitive therapy. *J Urol*. 2004;171:1520–1524.
11. D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med*. 2004;351:125–135.
12. Klotz L. Active surveillance with selective delayed intervention is the way to manage 'good-risk' prostate cancer. *Nat Clin Pract Urol*. 2005;2:136–142; quiz 1 p following 149.
13. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA*. 2005;294: 433–439.
14. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280:969–974.
15. Potosky AL, Reeve BB, Clegg LX, et al. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. *J Natl Cancer Inst*. 2002;94:430–437.
16. Litwin MS, Gore JL, Kwan L, et al. Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. *Cancer*. 2007;109:2239–2247.
17. Arredondo SA, Downs TM, Lubeck DP, et al. Watchful waiting and health related quality of life for patients with localized prostate cancer: data from CaPSURE. *J Urol*. 2004; 172(5 pt 1):1830–1834.
18. Klotz L. Active surveillance with selective delayed intervention: using natural history to guide treatment in good risk prostate cancer. *J Urol*. 2004;172(5 pt 2):S48–S50; discussion S50-S51.

19. Klotz L. Active surveillance with selective delayed intervention for favorable risk prostate cancer. *Urol Oncol*. 2006;24: 46–50.
20. Epstein JI, Walsh PC, Carter HB. Dedifferentiation of prostate cancer grade with time in men followed expectantly for stage T1c disease. *J Urol*. 2001;166:1688–1691.
21. Freedland SJ, Kane CJ, Amling CL, Aronson WJ, Terris MK, Presti JC Jr. Upgrading and downgrading of prostate needle biopsy specimens: risk factors and clinical implications. *Urology*. 2007;69:495–499.
22. Emiliozzi P, Maymone S, Paterno A, et al. Increased accuracy of biopsy Gleason score obtained by extended needle biopsy. *J Urol*. 2004;172(6 pt 1):2224–2226.
23. Latini DM, Hart SL, Knight SJ, et al. The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *J Urol*. 2007;178(3 pt 1): 826–831; discussion 831–832.
24. Hruby G, Choo R, Klotz L, et al. The role of serial transrectal ultrasonography in a 'watchful waiting' protocol for men with localized prostate cancer. *BJU Int*. 2001;87:643–647.
25. Warlick C, Trock BJ, Landis P, Epstein JI, Carter HB. Delayed versus immediate surgical intervention and prostate cancer outcome. *J Natl Cancer Inst*. 2006;98:355–357.
26. Venkitaraman R, Norman A, Woode-Amissah R, et al. Predictors of histological disease progression in untreated, localized prostate cancer. *J Urol*. 2007;178:833–837.
27. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA*. 1994;271:368–374.
28. Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent: an update of the Johns Hopkins experience. *J Urol*. 2007;178:2359–2364; discussion 2364-2365.
29. Bailey DE, Mishel MH, Belyea M, Stewart JL, Mohler J. Uncertainty intervention for watchful waiting in prostate cancer. *Cancer Nurs*. 2004;27:339–346.
30. Roemeling S, Roobol MJ, Postma R, et al. Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance. *Eur Urol*. 2006;50:475–482.