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Prostate Cancer

Active Surveillance for Prostate Cancers Detected in Three Subsequent Rounds of a Screening Trial: Characteristics, PSA Doubling Times, and Outcome

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Abstract

Objectives: To study active surveillance as a management option for the important number of prostate cancer patients who would not have been diagnosed in the absence of screening.
Patients and methods: We analyzed baseline characteristics and outcome parameters of all men on active surveillance who were screen-detected in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Recruitment and surveillance of men were not guided by a protocol but depended on individual decisions of patients and their physicians.
Results: Active surveillance was applied in 278 men detected by screening from 1993 to 2006. At diagnosis, their median age was 69.8 yr (25–75p; 66.1–72.8); median PSA 3.6 ng/ml (25–75p; 3.1–4.8), and the clinical stage was T1c in 220 (79.1%) and T2 in 58 (20.9%). During the follow-up of median 3.4 yr, 103 men (44.2%) had a PSA doubling time that was negative (ie, half-life) or longer than 10 yr. Men detected at rescreening were significantly more likely to be on active surveillance, and they had more beneficial characteristics. Deferred treatment was elected in 82 cases (29.0%). Overall survival was 89% after 8 yr; the cause-specific survival was 100%.
Conclusions: This report shows a beneficial, although preliminary, outcome of screen-detected men managed on active surveillance. Men were more likely to be on active surveillance if the disease was detected at repeated screening. The report also shows that an important proportion of men have prolonged PSA doubling times, although the value of this parameter has not been established in untreated men.

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1. Introduction

Prostate cancer is an important cause of death in males. After lung cancer it is the second most important cause of cancer-related death in American males [1]. With the introduction of prostate-specific antigen (PSA) in the late 1980s, a screening tool became available that has been proven to detect prostate cancers earlier in the course of the disease [2]. One of the downsides of screening is a frequent diagnosis of low-risk cancers that would not have been detected during the man's lifetime in the absence of screening (ie, overdiagnosis). As screening becomes globally more prevalent, the side effects such as overdiagnosis will increase as well. It can be calculated that, if all US men with PSA levels $\geq$2.5 ng/ml would be biopsied, 775,000 cancers would be diagnosed, which is 542,910 more than the estimated 232,090 cases to be diagnosed in 2005 in the United States and 25.6 times more than the 30,350 men expected to die of the disease [3]. A large proportion of these men will have insignificant cancers. Although men with these cancers are likely to die as a result of other causes, the majority of them are currently treated [4].

Active surveillance focuses on men for whom therapy is delayed until the tumor becomes progressive and curative treatment can be offered. It is distinct from watchful waiting as described in currently used guidelines in that the former has a curative intent [5]. Although several studies have examined the role of watchful waiting prior to the widespread use of PSA [6–8], the natural course of screen-detected prostate cancer is less well-known [9,10]. Screen-detected prostate cancer differs from clinically diagnosed cancer. This is among other factors caused by lead- and length-time sampling bias.

Arguments to elect active surveillance include quality-of-life issues, costs associated with treatment, and ethical aspects. Little is known about the quality of life regarding active surveillance strategies. The SPCG-4 study has shown that the assignment of patients to watchful waiting or radical prostatectomy entails different risks of erectile dysfunction, urinary leakage, and urinary obstruction, but that, on average, the choice has little if any influence on well-being or the subjective quality of life after a mean follow-up of 4 yr [11]. Another argument is the costs of treatment. Although no literature is available, it seems obvious that active surveillance is less expensive than immediate treatment. The most important argument for active surveillance is probably an ethical argument: Our profession needs to decide what it considers an acceptable number of patients who need to be treated to prevent one prostate cancer death [12]. If any, the number of life-years gained will be small because of the fact that prostate cancer is a disease of older age. The potential benefit should be contrasted to the side effects of all applied treatments [13,14].

To investigate the natural course of prostate cancers detected by screening, this report describes the baseline characteristics, PSA kinetics, deferred treatment, and outcome of all men diagnosed with prostate cancer within the first, second, and partial third screen rounds of the European Randomized Study of Screening for Prostate Cancer (ERSPC), section Rotterdam, who were initially managed with active surveillance.

2. Methods

The ERSPC was designed to study the feasibility of population-based screening for prostate cancer and its effect on prostate cancer mortality. Therefore, by the end of 2002, 183,000 men were randomized in eight European countries starting in 1993 [15]. In the Netherlands alone, 42,376 men were randomized to the screen (n = 21,210) or the control arm (n = 21,166) from June 1993 through December 1999. Men in the screening arm were enrolled in a screening program with a 4-yr interval. From start until May 1997 men were offered a lateral sextant biopsy if either the PSA level was $\geq$4.0 ng/mL, or the digital rectal examination (DRE) and/or the transrectal ultrasound (TRUS) was suspect for carcinoma. From 1997, only a PSA $\geq$ 3.0 ng/mL prompted a lateral sextant biopsy, and DRE and TRUS were omitted as screening tests. A seventh lesion-directed biopsy core was taken in case of a hypoechogenic lesion.

2.1. *Study population*

This observational study describes a cohort of men on active surveillance who were detected within the screening program of the Rotterdam section of ERSPC. All men retrospectively met the following criteria:

1. Clinical stage T1c or T2 disease
2. PSA at diagnosis of 15 ng/mL or less
3. Biopsy Gleason score less than 8

The cutoff date for this analysis was 1 January 2006. By then, the first and second rounds of the Rotterdam section of the ERPSC were completed; the third round will be finished in December 2007. The choice of initiating and continuing an active surveillance policy was patient desire and/or physician advice. These criteria resulted in a study group of 278 men initially managed by active surveillance.

2.2. *Endpoints*

The primary endpoint of this analysis was prostate cancer mortality. Within ERSPC, an independent committee performs the review of all deceased prostate cancer patients with three

reviewers (a surgeon, a urologist, and a medical epidemiologist) who separately judge the anonymous patient charts [16]. The secondary endpoints of this study were overall mortality and change of therapy. For active surveillance practices, PSA progression does not serve as an endpoint but may serve as a trigger point to treatment.

2.3. Follow-up

Because follow-up regimens varied among local practices, data for this study were collected from semiannual patient chart reviews for the first 5 yr and annually thereafter. Charts were assessed for medical history, physical examination (DRE), dissemination studies, and PSA tests.

2.4. Statistics

To calculate PSA doubling time, the base 2 logarithm of the PSA value was calculated with the formula 2log(PSA) – 10log(PSA)/10log(2) and plotted against time since diagnosis (date of PSA measurement to date of diagnosis). The linear regression line through these points estimates the PSA slope. The doubling time can be calculated as the reciprocal value of a positive slope, while a negative or decreasing slope represents PSA half-life. PSA slopes were calculated in only patients with three or more PSA values acquired prior to a possible therapy change. For statistical analysis the commercially available software Statsitical Package for the Social Sciences, version 12.0.1 (SPSS, Inc, Chicago, IL, USA) was used. p values <0.05 were considered significant. The survival analyses for disease-specific and overall survival, and for deferred treatment-free survival were calculated by the Kaplan-Meier method.

3. Results

3.1. Baseline characteristics

From 1993 through 1999, 21,210 men were randomized to the screen arm of the Rotterdam section of the ERSPC. During the first round of screening, 1078 men were diagnosed with prostate cancer (Fig. 1). Of those, 106 men (9.8%) elected active surveillance. In the second screening round, 550 prostate cancers were detected, and 134 (24.4%) of the men elected active surveillance. In the incomplete third round, 144 prostate cancers have been diagnosed, and 38 men (26.4%) have elected active surveillance. Of the 1772 cancers detected in the first, second, and third rounds, 278 men (15.7%) elected active surveillance. At diagnosis, the study population had a median age of 69.8 yr and a median PSA level of 3.6 ng/mL. In 220 men (79.1%) the clinical stage was T1c; clinical stage T2 was present in 58 (20.9%). The initial PSA level for men diagnosed with prostate cancer at repeated screening was significantly lower. The other baseline characteristics, which

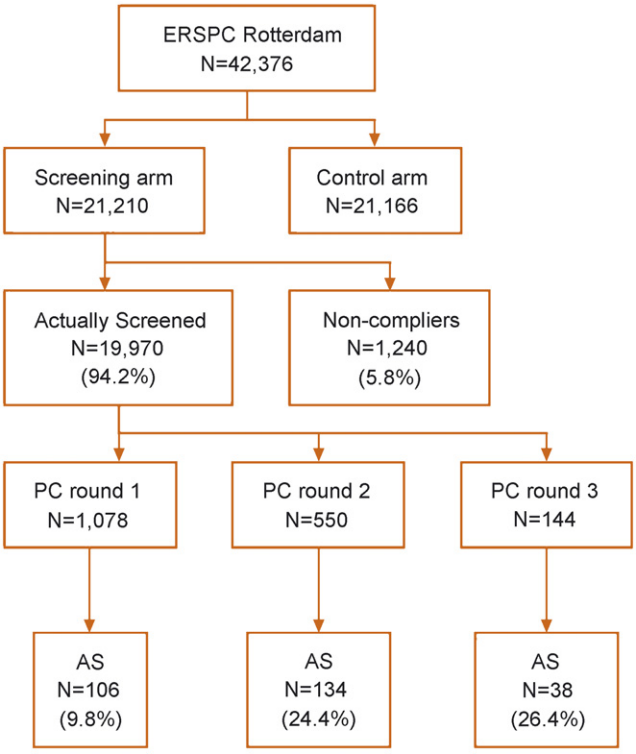

Fig. 1 – CONSORT diagram of men screened for prostate cancer in the first three screening rounds of the Dutch branch of the European Randomized Study of Screening for Prostate Cancer. PC = prostate cancer; AS = active surveillance.

are shown in Table 1 were not significantly different. The median follow-up time was 3.4 yr: 6.0 yr for round 1 men, 3.2 yr for round 2, and 1.2 yr for those detected in round 3.

3.2. Deferred treatment

Of 278 men initially managed on an active surveillance policy, 82 (29.0%) received deferred treatment after a median of 2.5 yr (25th and 75th percentiles [25–75p]: 1.3–5.0, Table 2). Deferred radical prostatectomy was performed in 13 men (15.9%). Radiotherapy was administered in 56 men (68.3%). The remainder (n = 13; 15.9%) received hormonal treatment. The 5-yr deferred treatment-free survival was 70.8% (Fig. 2). After deferred radical prostatectomy, one man had capsular penetration (pT3A) and four had positive margins (Table 3).

3.3. PSA doubling time

Table 4 shows that the initial PSA level and the PSA doubling time, while not a predetermined reason for changing to deferred treatment, had a significant

Table 1 – Characteristics at diagnosis of men on active surveillance in three subsequent screen rounds

		R I	R II	R III*	Total	*p* value
PC	Number	1,078	550	144	1,772	
AS	Number (%)	106 (9.8)	134 (24.4)	38 (26.4)	278 (15.7)	<0.001†
Age (yr)	Median (25–75p)	69.4 (65.7–72.4)	69.9 (65.9–73.1)	70.5 (67.3–73.3)	69.8 (66.1–72.8)	0.45‡
PSA (ng/mL)	Median (25–75p)	4.2 (3.3–5.5)	3.4 (2.6–4.4)	3.8 (3.3–5.6)	3.6 (3.1–4.8)	<0.001†
	0–5	72 (67.9)	119 (88.8)	27 (71.1)	218 (78.4)	
	5–10	28 (26.4)	15 (11.2)	11 (28.9)	54 (19.4)	
	>10	6 (5.7)	0 (0.0)	0 (0.0)	6 (2.2)	
Clinical stage	T1C	83 (78.3)	113 (84.3)	24 (63.2)	220 (79.1)	0.21†
	T2	19 (17.9)	21 (15.6)	14 (36.8)	58 (20.9)	
Biopsy Gleason	≤6	98 (92.5)	127 (94.1)	37 (97.4)	262 (94.2)	0.50†
	7	8 (7.5)	7 (5.2)	1 (2.6)	16 (5.8)	
Cores with PC (number)	1–2 (%)	91 (85.8)	111 (82.8)	34 (89.5)	236 (84.9)	0.82†
	3–4 (%)	14 (13.2)	20 (14.9)	3 (7.9)	37 (13.3)	
	5–7 (%)	1 (0.9)	3 (2.2)	1 (2.6)	5 (1.8)	

R I = round 1; R II = round 2; R III = round 3; PC = prostate cancer; AS = active surveillance; 25–75p = 25th and 75th percentiles.
* Round 3 will be completed in December 2007.
† Chi-square test.
‡ Kruskal-Wallis test.

relationship with that decision, in contrast to the last PSA level before treatment. A total of 1799 PSA tests were performed, with a median of four tests per patient (25–75p: 2–7 tests). The PSA doubling time was calculated for 234 men with three or more PSA tests. A PSA doubling time that was longer than 10 yr or negative (ie, PSA half-life) was noted in 21.4% and 22.6%.

3.4. *Outcome*

Twenty-six men (9.4%) died during follow-up but not from prostate cancer. After 8 yr, the prostate cancer-specific survival was 100.0% and the overall-survival was 84.0% (Table 2). Forty-three men (15.5%) were still at risk after 8 yr; 26 (60.5%) of those had not received any treatment for their prostate cancer.

Table 2 – Follow-up characteristics of men detected in three subsequent screening rounds who were managed on active surveillance

		R I	R II	R III	Total	*p* value
AS	No.	106	134	38	278	
Follow-up (yr)	Median (25–75p)	6.0 (3.4–7.9)	3.2 (2.1–4.5)	1.2 (1.2; 0.0–3.3)	3.4 (1.8–6.0)	<0.001*
PSA DT	0–2 yr	2 (2.2)	11 (9.2)	4 (17.4)	17 (7.3)	0.02†
	2–4 yr	9 (10.0)	20 (16.7)	3 (13.0)	32 (13.7)	
	4–6 yr	23 (25.6)	20 (16.7)	2 (8.7)	45 (19.3)	
	6–8 yr	14 (15.6)	8 (6.7)	1 (4.3)	23 (9.9)	
	8–10 yr	6 (6.7)	7 (5.8)	0 (0.0)	13 (5.6)	
	>10 yr	22 (24.4)	21 (17.5)	7 (30.4)	50 (21.5)	
	Negative	14 (15.6)	33 (27.5)	6 (26.1)	53 (22.7)	
	N/A	16	14	15	45	
Treatment change	RP	8 (7.5)	4 (3.0)	1 (2.6)	13 (4.9)	0.05†
	RT	27 (25.5)	25 (18.7)	4 (10.5)	56 (20.1)	
	HT	9 (8.5)	4 (3.0)	0 (0.0)	13 (4.9)	
	Total	44 (41.5)	33 (24.6)	5 (13.2)	82 (29.0)	
Time to treatment (mo)	Median (25–75p)	3.9 (1.6–6.4)	2.0 (1.2–4.0)	1.2 (0.7–2.0)	2.5 (1.3–5.0)	0.03*
Mortality	All causes	18 (17.0)	8 (6.0)	0 (0.0)	29 (10.2)	0.001†
	PC	0	0	0	0 (0.0)	
Overall survival‡	5 yr	87.2	91.9		89.0	0.45§
PC survival‡	5 yr	100.0	100.0	100.0	100.0	

R I = round 1; R II = round 2; R III = round 3; AS = Active surveillance; PSA DT = PSA doubling time; RP = radical prostatectomy; RT = radiotherapy; HT = hormonal treatment; PC = prostate cancer; N/A = Not available; less than three PSA values.
* Kruskal-Wallis test.
† Chi-square test.
‡ Kaplan-Meier method.
§ Log-rank test for trend.

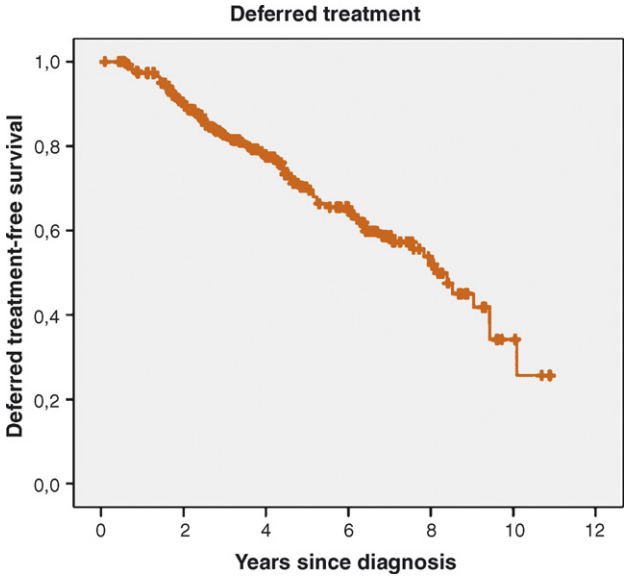

Fig. 2 – Kaplan-Meier projection of deferred treatment free survival (N = 263).

Follow-up (yr)	0	2	4	6	8	10
Men at risk	263	200	122	71	26	3
Deferred treatment	0	34	51	67	77	82
DTFS (%)	100	86	78	66	53	31

DTFS = deferred treatment-free survival.

4. Discussion

Of men diagnosed at the prevalence (ie, first) screening of the ERSPC screening program, 10.2% were safely managed by active surveillance: During the median follow-up of 6 yr, 18.1% had died, all of intercurrent diseases. Men diagnosed at repeated screening had more beneficial characteristics and were more likely to elect active surveillance. The latter is the result of an ongoing stage and grade shift, but is likely to be influenced by a time trend as well. Active surveillance has become a more popular management option for prostate cancer in the Netherlands. Men on active surveillance had PSA doubling times that were longer than 10 yr or negative in 43.7% of cases. Although this finding suggests insignificant cancer, the value of PSA kinetics in evaluating untreated screen-detected prostate cancer patients is still unclear.

It is currently difficult to risk stratify men well enough and with acceptable confidence intervals, although better and more individual predictors for outcome are being developed. This study shows that men with Gleason score 7 might well be good candidates to systematically keep their cancers under surveillance until they die from other causes. Vis et al [17] showed in a radical prostatectomy series that the proportion of high-grade Gleason pattern in a biopsy was superior to the currently used Gleason score. Another step toward a more personalized risk prediction of potentially indolent prostate cancer is the development and use of nomograms [18,19]. The window of opportunity for active surveillance strategies is unknown; however, on the basis of incidence-to-mortality ratios, it is likely to be larger than the number of men included in watchful waiting and active surveillance cohorts published so far [6,7,20,21]. Tumors that have a high probability to be indolent could appear to be important prostate cancers because of biopsy undersampling and dedifferentiation [22]. However, in light of the minimal improvement in cancer-specific survival when comparing surgical treatment to no treatment among men with cancers not detected by screening [23], it seems unlikely that active surveillance of low-risk, screen-detected cancers will place patients at undue risk of an adverse outcome. Two studies [24,25] could not find adverse effects of prolonged delays on the outcome

Table 3 – Pathologic characteristics of men with deferred radical prostatectomy

PSA at diagnosis (ng/mL)	Median (25–75p)	4.2 (3.1–5.9)
Clinical stage	cT1C	10
	cT2A	3
Biopsy Gleason score	<7	12
	≥7	1
PSA before surgery	Median (25–75p)	6.6 (5.0–7.4)
Pathologic stage*	pT2A	1
	pT2C	9
	pT3A	1
	N1	0
Gleason score	<7	9
	7	2
Margin status	Positive	4

PSA = prostate-specific antigen; 25–75p = 25th and 75th percentiles.
* According to Schroder FH, Hermanek P, Denis L, et al. The TNM classification of prostate cancer. Prostate Suppl 1992;4:129–38.

Table 4 – Prognostic factors for freedom of deferred treatment

		5-yr DTFS (%)	Log-rank test
iPSA	≤5.0	75.2	0.03
	>5.0	57.9	
Last PSA	≤10.0	72.1	0.92
	>10.0	68.8	
PSA DT	<3 yrs	35.6	<0.0001
	3–5 yrs	47.6	
	5–10 yrs	86.7	
	>10 yrs	96.2	
	Negative	91.2	

iPSA = initial prostate-specific antigen; 5-yr DTFS = 5-yr deferred treatment-free survival; PSA DT = PSA doubling time.

after radical prostatectomy for men enrolled in their active surveillance programs. The current cohort differs from that in the Scandinavian study in both the recruited population and the intent of expectancy. The research challenge for the years to come lies in optimizing risk prediction.

It is difficult to identify the reasons why patients and/or doctors elect deferred radical treatment. Anxiety in patients seems to be an important factor in the decision to change to active treatment [11]. It would be a big advance if variables predicting anxiety in patients could be identified and used to risk stratify patients. Offering men a support program could be of help [26]. Rapid rising PSA values are only assumed to predict metastases and eventually death from prostate cancer. The predictive value of PSA doubling time as a predictor for prostate cancer death is based mainly on radical prostatectomy series, and there is no direct evidence to support this relationship in the natural course of screen-detected prostate cancer [27]. McLaren et al [28] showed that, on multivariate analysis, PSA doubling time strongly correlated with clinical progression ($p < 0.001$), stage progression ($p = 0.01$), and time to treatment ($p < 0.001$). An evaluation of PSA kinetics on a proper endpoint is important to further establish these correlations. Because of the absence of possible endpoints in our cohort, it is for the present not possible to further evaluate the predictive value of PSA doubling time. Even after 7 yr, almost a quarter of the men in our cohort have doubling times under 5 yr and show no signs of progression. In the cohort of Carter et al [21], the median PSA doubling time was 2.5 yr for those who underwent therapy and 25.8 yr for those remaining on watchful waiting.

Klotz [20] reported that, in a cohort of 299 patients, 65% remained free of treatment at 8 yr, which is more than the 52.0% in our study. During a follow-up of 3.8 yr, Carter et al [21] had 98 patients who remained on watchful waiting; 215 proceeded to treatment. A total of 57.3% and 73.2% chose treatment within the first 2 and 4 yr, respectively. In our cohort 29% elected deferred treatment with a lower 4-yr deferred treatment rate of 22%.

One should note that men detected by screening in our screening program have a calculated lead time of 11.2 yr (range: 10.8–12.1 yr) [29], which means that men are diagnosed a mean 11.2 yr before the cancer would be diagnosed clinically. An important proportion of these men are therefore eligible for active surveillance. We have to wait for the follow-up periods of 15 yr and beyond to draw more definitive conclusions. Current active surveillance programs, including the Rotterdam program, use standard repeat biopsies and more intensive biopsy sampling. All treatment decisions in the contemporary series were based on initial sextant biopsy sampling according to the ERSPC protocol; no standard repeat biopsies were scheduled. There is evidence that detection rates increase with the number of cores [30]. More importantly, obtaining more cores results in more adequate sampling and allows for increased risk stratification [31]. Furthermore it should be noted that a predetermined protocol for the enrolment and follow-up of men in an active surveillance strategy was not used; the outcomes described in this study are based on an observational study. Currently, a prospective study to assess the value of a fixed active surveillance program has been initiated in Rotterdam (ie, Prostate Cancer Research International: Active Surveillance [PRIAS]). Although these measures were not implemented at the time of follow-up of this cohort, the oncologic control was still optimal. This outcome taken together with current incidence-to-mortality ratios might support the view that entry criteria for active surveillance strategies could be wider than currently practiced.

5. Conclusions

Active surveillance plays an important role in the management of men with screen-detected prostate cancer detected within our screening program. Men detected at repeated screening are more likely to be on active surveillance. The cause-specific survival of our cohort was 100% at 5 yr. Although the exact value of PSA doubling time as a predictor of prostate cancer death needs to be established for untreated screen-detected men, an important proportion of men have prolonged PSA doubling times or even PSA half-lives, which are generally regarded as indicative of insignificant disease. Active surveillance seems to offer an important opportunity for the current overtreatment that results from screening.

Conflicts of interest

The authors have nothing to disclose.

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Editorial Comment

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Prostate-specific antigen (PSA) screening occurs at an alarming rate among men who will gain no benefit from the diagnosis or treatment of prostate cancer [1]. It has been estimated that 30–50% of men diagnosed with prostate cancer today by PSA testing would otherwise have not known they had cancer during life in the absence of screening (ie, overdiagnosis) [2,3]. Yet, >90% of men diagnosed with prostate cancer undergo some form of active treatment [4]. Thus, overtreatment of prostate cancer should be a major concern of the practicing urologist, and consideration of the need for treatment should be a part of the initial assessment of any patient with newly diagnosed prostate cancer.

The authors describe an alternative to immediate curative intervention called active surveillance or expectant management with curative intent in a small subset of men who were diagnosed in a screening program. Active surveillance should be thought of as an approach designed to identify those men at low risk of progression without treatment that involves careful follow-up so that if progression occurs, curative intervention can be delivered during a window of curability [5]. Criteria that have been used for selection of men for surveillance include older age or comorbidities that limit life expectancy, lower clinical stage, absence of high-grade disease, minimal cancer on biopsy, and PSA (absolute level and density). Follow-up of men on surveillance involves at least serial PSA measurements and digital rectal examinations, and some have recommended surveillance prostate biopsies. Triggers for curative intervention that have been described include local progression of disease, the finding of higher grade or more extensive disease on surveillance biopsy, and PSA kinetics (especially PSA doubling time [PSADT]).

In the current study, the authors did not apply a uniform approach to selection of candidates, follow-up, or triggers for intervention. They did find that when compared to all men, those selected for surveillance had lower PSA values and that a longer PSADT was significantly associated with a lower likelihood of deferred treatment. So even in the absence of specific triggers for intervention, PSA kinetics was used to determine the need for treatment in this population being managed expectantly. Although PSADT has been shown to be a surrogate for cancer-specific survival after curative intervention when PSA levels are consistently rising, there are no data to support the contention that a PSADT trigger will allow intervention at a time when cure is likely in men who have fluctuating values. In the absence of a biomarker for reliably detecting disease progression, I believe that men in a surveillance program should undergo surveillance biopsies.

Patients and physicians will become increasingly comfortable with active surveillance as a management option as we learn more about the natural history of screen detected prostate cancers. Goals for the future should be to identify reliable criteria for selection of those men for whom surveillance is safe and to identify triggers that will allow curative intervention in those men with progression when the disease is still curable.

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