



Prostate Cancer

Management and Survival of Screen-Detected Prostate Cancer Patients who Might Have Been Suitable for Active Surveillance

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ERSPC, European Randomized study of Screening for Prostate Cancer
 RP, Radical prostatectomy
 RT, Radiotherapy
 WW, Watchful waiting
 PC, Prostate cancer
 PSA, Prostate-specific antigen
 PSA D, Prostate-specific antigen density
 PCS, Prostate cancer specific

Abstract

Objective: Screening practices for prostate cancer have resulted in an increasing incidence of prostate cancers. Our knowledge about which prostate cancers are life threatening and which are not is limited. Thus, for ethical, medical, and economic reasons we need to define which patients can be managed by active surveillance.

Methods: From 1993 through 1999, men from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC) were screened by two strict protocols, which were based on prostate-specific antigen (PSA), digital rectal examination, and transrectal ultrasound. For this study, men with criteria that reflect current active surveillance studies were selected: those with a biopsy Gleason score $\leq 3 + 3$ in two or fewer cores, with a PSA density < 0.2 and a maximum PSA-level of 15 ng/ml. Clinical stage had to be T1c or T2.

Results: Of the 1,014 prostate cancers detected in the prevalence screen, 293 men (28.9%) met the criteria for active surveillance. Their mean age was 65.7 and the mean PSA level was 4.8 ng/ml. Radical prostatectomy was elected by 136 men (46.4%), radiotherapy by 91 (31.1%), and watchful waiting by 64 (21.8%). The mean follow-up was 80.8 months. The eight-year prostate cancer-specific survival was 99.2%; the overall survival was 85.4%. Nineteen men who chose watchful waiting changed to definitive treatment during follow-up.

Conclusion: Only three men died of prostate cancer, none of whom were on watchful waiting. Our observations provide preliminary validation of the arbitrary selection criteria for active surveillance.

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1. Introduction

Screening has caused a marked increase in prostate cancer incidence, although whether the stage and grade shift that has been caused by prostate-specific antigen (PSA)-based screening reduces the prostate cancer mortality is unclear. In the United States, it is estimated that 234,460 men will be diagnosed with, and 27,350 will die of prostate cancer in 2006 [1]. If the current trend towards using lower PSA-thresholds to determine the need for biopsy and towards taking more cores per biopsy continues, the prostate cancer incidence will continue to rise [2]. Most of the cancers diagnosed at low PSA-values are good risk, low-grade tumours, which would not have been diagnosed in the absence of screening (i.e. over-diagnosis) [3]. Although men with these cancers are likely to die as a result of other causes, the majority of them are currently treated.

The side-effects of prostate cancer treatment are substantial [4,5]. Therefore, the present challenge should be to identify the cancers that need treatment and those that do not. Active surveillance entails a strategy by which selected men are managed expectantly with the intention to apply potentially curative treatment if signs of progression occur. This goal should be achievable by means of PSA-kinetics, digital rectal examinations (DREs), and repeat biopsies. Expectancy is maintained until the patient dies of other causes, receives definitive treatment, or requests treatment. Active surveillance is still subject to studies. The inclusion criteria of such studies are, besides patient wish, based on the PSA-level, in combination with prostatic size, DRE, and the pathologic features of the biopsy [6]. This report describes the outcome and management of all men diagnosed with prostate cancer within the prevalence screen of the European Randomized study of Screening for Prostate Cancer (ERSPC), section Rotterdam who met criteria that are typically designed for an active surveillance program.

2. Methods

The ERSPC was designed to study the feasibility of population based screening for prostate cancer. Therefore, 183,000 men were randomized in eight European countries starting in 1993 [7]. 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. From the beginning until May 1997 men were offered a lateral sextant biopsy if either the PSA level was ≥ 4.0 ng/mL, or the DRE or transrectal ultrasound was suspicious for carcinoma. From 1997, only a PSA ≥ 3.0 ng/ml prompted a lateral sextant biopsy. PSA levels were determined

in all patients at diagnosis with the Beckman-Coulter Hybritech Tandem E Assay (Hybritech Incorporated, San Diego, California, USA), which was replaced after January 2000 by the automated version (Beckman-Access; Beckman-Coulter Inc., Fullerton, California, USA).

2.1. Definition

Watchful waiting entails a strategy for all men who are managed expectantly, whereas active surveillance focuses on men for whom therapy is delayed until the tumour becomes progressive and curative treatment can be offered. Men on watchful waiting who are not on active surveillance are mainly those who are too sick or too old for treatment. They receive endocrine treatment if indicated as in the SPCG-4 trial [8].

2.2. Study population

The criteria we considered acceptable for enrollment in an active surveillance protocol were: (1) a biopsy Gleason score $\leq 3 + 3$, (2) a maximum of two cores invaded with prostate cancer, (3) clinical stage T1C or T2, (4) a PSA density < 0.2 ng/ml/cc, and (5) a PSA level ≤ 15 ng/ml. The criteria we considered appropriate for active surveillance strategies were defined according to the literature; furthermore, they are based on analysis of the data ERSPC has generated so far [6,9,10]. The men who were diagnosed in the prevalence screen of the ERSPC and who met the criteria were selected as our study population.

2.3. Endpoints

The primary endpoint of this study was prostate cancer-specific 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 anonymised patient charts [11]. The review of men who were diagnosed in the first round of screening was complete until January 1, 2005. The secondary endpoints of this study were overall mortality, metastatic disease, and biochemical progression. Biochemical progression in radical prostatectomy patients was considered to be present when PSA was > 0.1 ng/ml and rising. For men treated with radiotherapy the ASTRO definition was used [12]. The date of progression was set at the median of the date of the first PSA rise and the previous PSA record date. For active surveillance PSA progression does not serve as an endpoint but as a trigger point to treatment. Therefore, no biochemical progression rates were calculated. The only man who received hormonal treatment had a stable PSA and thus showed no progression with any of the definitions of biochemical progression for hormonal treatment.

2.4. Follow-up

Patients were seen at three-month intervals within one year after therapy initiation; thereafter, twice yearly controls were performed at our institution and surrounding hospitals. At

each visit a serum PSA level was obtained, and a DRE was performed. PSA values that were obtained by other assays (in surrounding regional hospitals) were corrected for known differences with the Hybritech assay using the regression method of Passing and Bablok, as described by Yurdakul et al. [13]. The median follow-up was 79.4 months (mean 80.8; range 6.8–129.8) and was equal in the treatment arms.

2.5. Pathologic processing

Systematic, lateralized sextant biopsies were obtained during longitudinal and cross-sectional ultrasonographic scanning of the prostate [14]. A seventh, lesion-directed biopsy was taken in case of a hypo-echogenic lesion. Prostate biopsy cores were labelled and processed individually. One pathologist reviewed all biopsies and classified carcinoma, prostatic intraepithelial neoplasia, and lesions that were suspicious for malignancy.

Slides from radical prostatectomy specimens were retrieved from the archives of the pathology laboratories of our institution and surrounding hospitals. A single protocol for total embedding of the prostate was used in all pathology laboratories to allow accurate measurements of tumour volume, grading, and staging [15]. In short, after fixation, radical prostatectomy specimens were inked and serially sectioned at 4-mm intervals, and embedded totally in paraffin blocks. After a pathology review, pathologic disease stage, and Gleason score were determined [16]. Tumour volume was measured by morphometry, as described previously [17]. For tumour staging of radical prostatectomy specimens, the 1992 TNM classification system for prostate carcinoma was used [18].

2.6. Statistics

For statistical analysis the commercially available software SPSS was used (version 12.0.1; SPSS, Inc., Chicago, Illinois, USA). *P*-values <0.05 were considered significant. The survival

analyses for biochemical progression, metastatic disease, disease-specific, and overall survival were calculated by the Kaplan-Meier method.

3. Results

From 1993 through 1999, 21,210 men were randomised to the screen arm of the Rotterdam section of the ERSPC. During the first round of screening 19,970 men were screened and 1,014 were diagnosed with prostate cancer. Our study group consisted of the 293 men (28.9%) who met the criteria we defined as currently representative for active surveillance. At baseline, the study population had a mean age of 65.7 (range 55.0–75.3) and a mean PSA level of 4.8 ng/ml (0.3–15.0). In 186 patients (63.5%) the DRE was not suspicious for carcinoma (stage T1C).

Radical prostatectomy was elected by 136 men (46.4%), radiotherapy by 91 men (31.3%), and 64 (21.8%) were managed by watchful waiting. One man received hormonal treatment and in another patient no treatment was initiated, because he died very shortly after the prostate cancer diagnosis. The baseline characteristics are shown in Table 1.

3.1. Radical prostatectomy

Table 2 shows that the median volume of tumours found in 117 radical prostatectomy specimens was 0.24 ml (mean 0.49; range 0.001–4.71); in 34 prostates (29.1%) the tumour volume was >0.50 ml. In five prostates (3.9%) capsular perforation was present, vascular infiltration was present in two, and

Table 1 – Characteristics at baseline for all 293 patients with tumours that met the criteria for active surveillance

		RP	RT	WW	Total	<i>p</i> -value
Number		136 (46.4%)	91 (31.1%)	64 (21.8%)	293	(RP vs. WW)
Age	Mean ± sd	62.9 ± 4.1	67.9 ± 4.7	68.4 ± 4.5	65.7 ± 5.1	<0.001* (<0.001**)
PSA (ng/ml)	Mean ± sd	4.9 ± 2.5	5.2 ± 2.3	4.1 ± 1.5	4.8 ± 2.2	0.01* (0.05**)
	0–5	80 (58.8%)	49 (53.8%)	47 (73.4%)	178 (60.8%)	
	5–10	53 (39.0%)	38 (41.8%)	17 (26.6%)	108 (36.9%)	
	10–15	3 (2.2%)	4 (4.4%)	0 (0.0%)	7 (2.4%)	
PSA density	Mean ± sd	0.11 ± 0.04	0.11 ± 0.04	0.10 ± 0.04	0.11 ± 0.04	0.37* (0.16**)
Biopsy cores with PC	1	76 (55.9%)	43 (47.3%)	49 (76.6%)	169 (57.7%)	<0.001** (0.01**)
	2	60 (44.1%)	48 (52.7%)	15 (23.4%)	124 (42.3%)	
Clinical stage	T1C	83 (61.0%)	52 (57.1%)	50 (78.1%)	186 (63.5%)	0.02** (0.02**)
	T2	53 (38.9%)	39 (42.9%)	14 (21.9%)	107 (36.5%)	

RP: Radical Prostatectomy; RT: Radiotherapy; WW: Watchful Waiting; PSA: Prostate-Specific Antigen; PC: Prostate Cancer.

The *p*-values in the last column are the results of the statistical tests for the null-hypothesis that all three groups are part of the same population and thus not different. The *p*-values between brackets result from the statistical test of the null hypothesis that the RP and the WW group are not different from each other.

* Kruskal–Wallis test.

** Chi-square test.

*** Mann–Whitney *U* test.

Table 2 – Pathological features of radical prostatectomy specimens for the 136 patients who were treated with immediate radical prostatectomy

			n.a.
Tumour volume (ml)	Median (range)	0.24 (0.001–4.71)	18
	<0.2	51 (43.2%)	
	0.2–0.5	33 (28.0%)	
	0.5–1.0	20 (16.9%)	
	1.0–2.0	8 (6.8%)	
	>2.0	6 (5.1%)	
Pathological stage	pT0	1 (0.8%)	5
	pT2	122 (93.1%)	
	pT3	4 (3.1%)	
	pT4	4 (3.1%)	
Gleason score	≤6 (3 + 3)	108 (82.4%)	5
	7	21 (16.0%)	
	8–10	2 (1.5%)	
Capsular perforation		5 (3.9%)	7
Vascular invasion		2 (1.5%)	0
Seminal vesicle invasion		1 (0.7%)	0
n.a.: not available.			

seminal vesicle infiltration in one. Undersampling in Gleason score (undergrading) was present in 23 men (17.6%), of whom two (1.5%) had a Gleason score of the radical prostatectomy specimen 8–10 (5 + 4 = 9 and 5 + 3 = 8).

3.2. Radiotherapy

Radiotherapy was elected by 91 men: external beam radiotherapy by 88 and brachytherapy by three. The radiotherapy dosage varied from 64 Gray (one man), 66 Gray (41 men), 68 Gray (38 men) to 78 Gray (5 men). In three men, the dosage could not be retrieved. Brachytherapy was applied as monotherapy in one

of the three men, the other two received additional external beam radiotherapy, with dosages 45 and 68 Gray.

3.3. Watchful waiting

Of 64 men initially managed on a watchful waiting policy, 19 (29.7%) received deferred treatment after a median of 40.1 months (mean 38.9; range 9.1–78.6). Deferred radical prostatectomy was performed in two men; both had organ-confined disease. Radiotherapy was provided in 13 men, two of whom received high dose rate brachytherapy. The remainder received solely external beam radiotherapy (one patient 66 Gray, one patient 72 Gray, the remainder 68 Gray, all in portions of two Gray). Four men received hormonal treatment. The major reason for deferred treatment was an increasing PSA level.

3.4. Outcome

During a mean follow-up of 80.8 months, three men died from prostate cancer (one radical prostatectomy, two radiotherapy) and 40 died from intercurrent disease (Table 3). After eight years, the prostate cancer-specific survival was 99.2% and the overall survival was 85.4% (Fig. 1). The baseline characteristics of men who died from prostate cancer or developed metastases are stated in Table 4.

Metastatic disease developed in two men who elected radical prostatectomy and in two radiotherapy patients; three of those died as a result of prostate cancer. The fourth man was still at risk on December 1, 2005. His last PSA level was 555 ng/ml, but he was active and feeling well.

Biochemical progression was present in 13 radical prostatectomy patients (9.6%) and 16 radiotherapy patients (17.6%). The eight-year biochemical

Table 3 – Outcome for all 293 patients with tumours that met the criteria for active surveillance

	RP	RT	WW	Total
No.	136	91	64	293
PSA progression	13 (9.6%)	16 (17.6%)	–	29 (9.9%)
Metastatic disease	2 (1.5%)	2 (2.2%)	0 (0.0%)	4 (1.4%)
Death	14 (10.3%)	19 (20.9%)	9 (14.1%)	43 (14.7%)
5-year survival [†]	94.8%	90.0%	91.1%	93.2%
8-year survival [†]	91.3%	79.2%	85.3%	85.4%
Prostate cancer death	1 (0.7%)	2 (2.2%)	0 (0.0%)	3 (1.0%)
5-year PCS survival ^{**}	99.2%	100%	100%	99.6%
8-year PCS survival ^{**}	99.2%	98.6%	100%	99.2%

RP: Radical Prostatectomy; RT: Radiotherapy; WW: Watchful Waiting; PSA: Prostate-Specific Antigen; PCS: Prostate cancer specific.

[†] p-value 0.08 (log-rank test for trend).

^{**} p-value 0.26 (log-rank test for trend).

Table 4 – Characteristics of men who developed metastatic disease

		Patient 1	Patient 2	Patient 3	Patient 4
Characteristics at baseline	Treatment	RP	RP	RT	RT
	Clinical stage	T2A	T2A	T1C	T2A
	Cores prostate cancer	2	2	2	2
	PSA (ng/ml)	6.4	6.5	4.4	7.6
	PSA D (ng/mL/cc)	0.16	0.14	0.06	0.15
	Planimetric volume	40.9	46.2	67.9	49.6
	Age at diagnosis	68.8	69.8	73.4	74.1
RP specimen	Tumour volume (ml)	1.63	1.11		
	Gleason score	5 + 4 = 9	4 + 3 = 7		
	Vascular infiltration	Yes	No		
	Pathological stage	pT4a	pT4a		
Follow-up	Time to BP (months)	4.8	6.6	87.5	21.3
	Time to M+ (months)	38.9	49.8	109.1	57.2
	Time to death (months)	53.2	–	110.1	63.2

RP: Radical Prostatectomy; RT: Radiotherapy; PSA: Prostate-Specific Antigen; BP: Biochemical Progression; M+:Metastatic disease.

progression-free survival was 89.8% in radical prostatectomy, 71.7% in radiotherapy, and 100% in those who received active treatment after surveillance (log-rank test for trend: $p = 0.12$).

With a median follow-up of 82.4 months (mean 80.4; range 23.8–119.9), of 64 men initially managed with watchful waiting, none developed metastatic disease or died from prostate cancer. Without

having received definitive treatment for their prostate cancer, eight men (17.8%) died of other causes.

4. Discussion

This study describes the treatment and follow-up of screen-detected prostate cancer patients with baseline characteristics that are currently regarded as suitable for active surveillance. Men were treated by radical prostatectomy, radiotherapy, or watchful waiting. The high disease-specific survival (99.2% after eight years) is in sharp contrast with the overall survival of 85.4%.

The follow-up of the watchful waiters showed that the natural course of these selected cancers is favourable. In addition, the radical prostatectomy specimens showed disease characteristics of men who met the active surveillance criteria as well. Although the prognostic factors of the radical prostatectomy group were significantly less favourable than those in the watchful waiting group, this probably only results in an overestimation of these factors in the watchful waiting group. As a result, the real pathological features at the time of diagnosis of men in the watchful waiting group are likely to be more favourable than suggested.

The cohort we described consists of men aged 55–74 who took part in the prevalence screen. They were screened for the first time and represent a large group of men in the general population. Within ERSPC Rotterdam, men are re-screened after four years. Re-screening has been described to result in an ongoing downstaging of tumours [19]. Therefore, the proportion of men who are suitable for active surveillance will only increase when men have had a

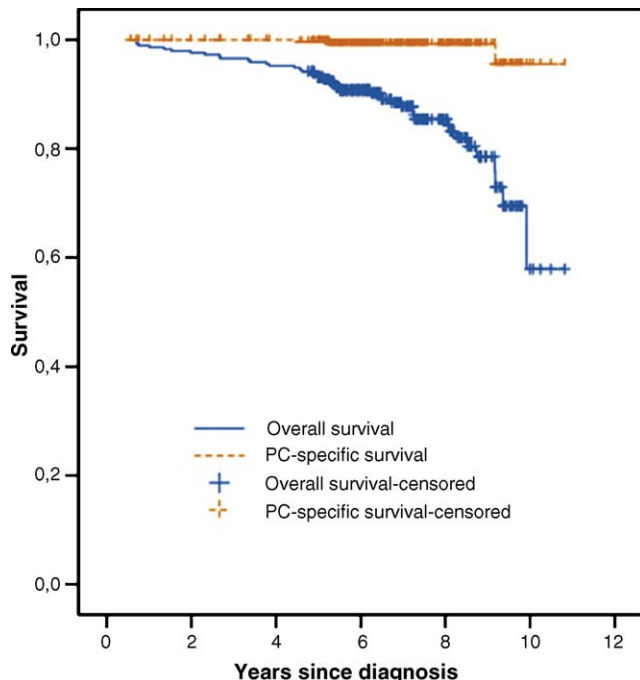


Fig. 1 – Kaplan-Meier graph of the overall and disease-specific mortality.

Time (years)	0	2	4	6	8	10
Men at risk	293	286	279	190	81	4
PC-spec (%)	100	100	100	99.2	99.2	95.6
Overall (%)	100	97.6	95.2	90.8	85.4	57.9

previous PSA recording. An important part of these men diagnosed with prostate cancer would not have developed symptoms of their prostate cancer in the absence of screening (i.e., overdiagnosis). Evidently, overdiagnosis is an important issue in current screening practices, although it is difficult to estimate its amount, which is, among other factors, dependent on the intensity of screening. Draisma et al. described the results of a computer estimation that used the ERSPC Rotterdam data [20]. They came to an overdiagnosis rate of 27%–56% for men aged 55–77 who were screened once. Until new biomarkers become available, PSA will be used as a screen test; the future results of screening studies in Europe and the United States are destined to influence the intensity of PSA testing more than the question of whether the test should be used for screening purposes at all [21]. The current challenge lies therefore in selecting cancers that do not need treatment, or at least not at the time they are diagnosed. Thus, overtreatment that results from overdiagnosis is minimized and treatment-related toxicity can be avoided [4,5].

The objective of active surveillance policies should be to include men for whom it seems safe to defer treatment; during the period of surveillance men with more aggressive, significant disease should be filtered out and offered definitive treatment. Deferred treatment should not be considered a failure of active surveillance as a management strategy. The expectation is that most men will die as a result of intercurrent disease without being treated. In our cohort 14.1% of men initially managed on a watchful waiting policy have already died of other causes; no metastatic disease developed. The prostate cancer-to-intercurrent death ratio in this study was three of 41 (7.0%), which means that for every man who dies of prostate cancer, more than 13 men with prostate cancer die of other causes. The overall life expectancy for Dutch men aged 65.5 is 15.4 years, which means they reach an age of 80.9 [22]. The mean age for men from our study group who were alive on January 1, 2005 was 72.3 (range 61.3–83.5); for the watchful waiters the mean age was 75.3 years (range 65.0–83.6). According to Pound et al., the median survival time from the development of metastatic disease after radical prostatectomy to death from prostate cancer was slightly less than five years [23]. Since all men who were initially managed on a watchful waiting policy were free from metastatic disease, it is unlikely that many men will die from prostate cancer.

One of the main challenges for active surveillance is to recognise the suitable patients. PSA should

certainly play a role in patient selection, but the possibility to differentiate more aggressive cancers is lost in the lower PSA ranges. Furthermore, the biologic variation of PSA in and between patients is large. The same holds for the value of the DRE, which has a poor positive predictive value, especially in the lower PSA ranges [24]. The third pillar of patient selection is in the pathological features of the biopsy specimen. More research is currently invested in adequate sampling of the prostate. The value of a uniform application of sextant biopsies in all prostates has been debated [25].

To find cancers with a certain volume and to estimate their actual grading in prostates of different sizes with a certain level of certainty, the number of biopsy cores should be individualized [26]. Unfortunately, few studies have investigated the prognostic value of the tumour volume on the outcome [27]. The undersampling rate is likely to increase with increasing prostatic size, although one study reported the opposite [28]. The radical prostatectomy specimens of men who met our active surveillance criteria beforehand illustrate the undersampling of prostates in our study: 6.1% of men had a pathological stage that was higher than the expected pT2, and 17.5% had a Gleason score that was higher than the expected 3 + 3 = 6. Both men in whom a radical prostatectomy was performed and subsequently developed metastases had a prostatic volume higher than the median volume of prostates included in our study group.

Retrospectively, it was evident that these men were undersampled and more biopsy cores should have been taken to allow a proper estimation of the tumour volume and grade. The biopsy table, which was proposed by Vashi et al., is likely to be a good scheme for estimating the number of biopsy cores needed in relation to prostatic size [29]. Extensive sampling of the prostate estimates tumour volume with reasonable precision [30]. On the other hand, more extensive sampling of the prostate will result in a higher incidence of prostate cancer. Many of the additionally found cancers will be insignificant and will increase the proportion of overdiagnosis.

5. Conclusion

Among those men who fulfilled our eligibility criteria for active surveillance, the natural course of the disease could be investigated in 64 patients. After a mean follow-up of 80.8 months, already 14.1% of men who were initially managed with watchful waiting have died of other causes; con-

trusted to the development of zero metastases. Our eligibility criteria could be validated in 136 men who underwent radical prostatectomy. Although further follow-up will be necessary, this study shows that prostate cancer patients who match the selection criteria applied in this study might be safely managed by active surveillance. However, under-sampling is still a problem. Therefore, appropriate prostate sampling, with respect to the prostatic size, at the time of diagnosis and during follow-up is essential.

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