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Tumour Features in the Control and Screening Arm of A Randomized Trial of Prostate Cancer

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Abstract

Objective: To compare tumour characteristics at the time of diagnosis of cancers detected in the screening and control arm at the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC).

Methods: Data were retrieved from the Rotterdam section of the ERSPC. Men were randomized to the screening arm ($n = 21{,}210$) or the control arm ($n = 21{,}166$). Men randomized to screening were offered PSA testing every 4 years. Through linkage with the cancer registry, men randomized to the control arm were detected. The biopsy Gleason score was determined in 1,591 and 373 patients in the screening and control arm, respectively. TURP, radical prostatectomy (RP) and cystoprostatectomy were evaluated for Gleason score, pathological (p)T stage and tumour volume.

Results: More prostate cancers were detected in the screening arm (15.9 vs. 4.2 per 1000 man years, $p < 0.0001$). Clinical stage distribution as well as biopsy and RP Gleason score distribution were significantly less favourable in the control arm. The incidence in man years of advanced disease (i.e. T4/N1/M1) was higher in the screening arm (6.0 per 100,000) as compared to the control arm (4.6 per 100,000). The 5-year PSA progression free survival after RP was 68% in the control arm and 89% in the screening arm ($p < 0.0001$). The proportion of Incidental prostate cancers was 9.3% of all cancers detected in the control arm.

Conclusions: Although the number of men with advanced prostate cancer is slightly higher in the screening arm, the proportion of prostate cancers with favourable features is increased in the screening arm as compared to that in the control arm.

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1. Introduction

The changing incidence in prostate cancer in the Western world is mainly due to PSA driven testing and the increase in life expectancy. PSA screening is thought to be a powerful tool to detect prostate cancer in an early stage, while curable [1]. The primary goal of the European Randomized study of Screening for Prostate Cancer (ERSPC) is to evaluate whether population based screening reduces mortality from prostate cancer at an acceptable price in terms of quality of life and costs [2,3]. It is expected that at the end of 2009 conclusive data on the influence of screening on prostate cancer mortality by comparison of both trial arms of the ERSPC will be available.

Comparison of histopathological features of prostatectomies performed on men of the screening arm of the ERSPC with those of a historical control group [4] of the same hospital demonstrated a decreased frequency of lymph node positive disease and a relative increase in proportion of Gleason score 8–10 cancers. However, a comparison of pathological features of all cancers detected in the screening and control arm of the Rotterdam section of the ERSPC was not reported previously.

Incidentally identified prostate cancer can be detected in approximately 10% of trans-urethral resection of the prostate (TURP) specimens. Tumours classified as pT1a diagnosed at TURP are considered as clinically indolent and with low biological potential with favourable follow-up and therefore they are usually managed by watchful waiting [5]. Detection of a substantial proportion of pT1a prostate cancers in the control arm may increase the prostate cancer specific survival in the control arm. Incidental prostate cancer may be detected in about 40% of cystoprostatectomy specimens obtained from men treated for a bladder cancer. These prostate cancers mostly have prognostically favourable features [6].

The present analysis of histopathological features of cancers detected within the control and trial arm of the Rotterdam section of the ERSPC was performed to demonstrate whether population based screening for prostate cancer would lead to the increased detection of prostate cancers with favourable and unfavourable characteristics.

2. Material and methods

2.1. *Patients and screening strategies*

In the Rotterdam section of the European Randomized Screening Study for Prostate Cancer (ERSPC) 42,376 men, 55–75 years old, were randomized to a screening (n = 21,210) and a control arm (n = 21,166). The follow-up of prostate cancer detection in the control arm was complete until the 1st of July 2003. Information on prostate cancer of men in the control arm was obtained through a record linkage with the Dutch cancer registry. Prostate cancer incidence was calculated per 1000 man-years. Man-years were calculated as the interval between dates of randomization to the cut-off date of 1st of July-2003. The cut-off date was overruled if death, prostate cancer diagnosis or the age of 75 occurred before the cut-off date. In the screening arm, 36 prostate cancers were diagnosed after the age of 75 years (outside screening protocol) and 108 cases were detected within the 4-year screening intervals (interval cancers). In the control arm 107 men were older than 75 years of age at prostate cancer diagnosis. Patients detected as interval cancers and patients diagnosed with cancer older than 75 years of age (in both arms) were excluded in this study. A manuscript describing the features of interval cancers is in preparation.

The details of the screening algorithm of the screened population have been described elsewhere [7]. In short, initially men were offered a PSA test, digital rectal examination (DRE) and transrectal ultrasonography (TRUS). Sextant needle biopsy was recommended for participants who had an elevated PSA level ($\geq$4.0 ng/ml), abnormal DRE or abnormal findings on TRUS. The protocol was simplified on May 1997, when sextant biopsy was recommended if PSA was $\geq$3.0 ng/ml, regardless of DRE and/or TRUS findings.

Patients of the screening arm were selected from the 1st, interim (performed one year after the 1st round in men with benign 1st round biopsy outcome), 2nd and 3rd screening round. Both the 2nd and 3rd rounds were not completed at the cut-off date. All diagnoses were based on histological examination. Slides from TURP and radical prostatectomy specimens, Millin prostatectomies, cystoprostatectomies, and prostate biopsies of the ERSPC participants were retrieved from the archives of the pathology laboratories of the Erasmus Medical Centre and surrounding hospitals of the Rotterdam region. One single protocol for total embedding of the prostate was in use in all pathology laboratories allowing accurate measurements of tumour volume, grading and staging [8]. In case of full compliance with the protocol, the tumour volume was measured. In short, radical prostatectomy specimens were inked and serially sectioned at 4 mm intervals and totally embedded in paraffin blocks. After review, pathologic stage (TNM 1992 classification) [9] and Gleason score [10] were determined by two uro-pathologists (T.H.v/d K. and G.J.L.H.v L.). Tumour volume was measured by morphometry as described previously [9]. Tumour volume could be determined in 44 and 470 radical prostatectomy specimens of the control and screening arm, respectively. Ten radical prostatectomy specimens and 4 TURP specimens of patients in the control arm could not be retrieved. Five men initially diagnosed with prostate cancer in the control arm did not have cancer after review. Even after immunohistochemistry was performed on these slides, prostate cancer could not be diagnosed. High-grade prostatic intra-epithelial neoplasia (PIN) and a lesion suspicious for prostate cancer was diagnosed in two and one man, respectively. These cases

were excluded from analysis. Treatment decisions were not under the control of the ERSPC trial.

Statistical analysis was done with the SPSS software package (SPSS 11.0 Inc., Chicago, IL). $p < 0.05$ was considered significant. Student *T*-test was used for linear variables, i.e. PSA and age. The Mann-Whitney *U* test was used for non-parametric data (tumour volume). The Kruskall-Wallis test was used for ordinal data. The Kaplan-Meier method was used to calculate PSA-progression free survival curves and significant differences between curves were based on the log-rank statistic.

3. Results

3.1. *Prostate cancer incidence*

Until July 2003, a total of 1,596 and 464 of prostate cancers were diagnosed, which corresponded to a cumulative incidence of 7.5% and 2.2% in the screening and control arm, respectively. In man-years, the incidence in the screen and the control arm was 15.9 and 4.2 per 1000 men years, respectively ($p < 0.0001$).

3.2. *Pre-treatment tumour characteristics*

Patients in the control arm had significantly higher PSA levels at prostate cancer diagnosis and a lower proportion of clinical T1c prostate cancer, compared to the screening arm (Table 1). The distribution of Gleason scores of sextant biopsies in the control arm showed a significantly higher proportion of Gleason score >7 cancer compared to the screening arm. The absolute number of (clinically) advanced disease (T4N0M0/TXN1M0/TXN0M1) was higher in the control arm (47 vs. 36).

3.3. *Therapy and pathological tumour characteristics*

Table 2 lists the therapy choices of patients of the screening and control arm. Curative therapy (i.e. radiotherapy and RP) was offered to 81.9 and 54.7% of patients in the screening and control arm, respectively. RP was performed in 37.3 and 18.1% of the patients in the screening and control arm, respectively. RP was abandoned because frozen sections on lymph nodes were positive for prostate

Table 1 – Patient, pre-treatment and tumour characteristics

	Screening arm *n* (%) *n* = 1596	Control arm *n* (%) *n* = 464	*p*-Value
Age (years)	66.5	67.9	$p < 0.0001$
PSA (ng/ml) mean, median (range)	8.6, 4.9 (0.3–315.7)	57.2, 11.0 (0.3–1500.0)	$p < 0.0001$
Clinical T stage *n* (%)			$p < 0.0001$
T1c	685 (42.9)	117 (25.2)	
T2	530 (33.2)	112 (24.1)	
T3	196 (12.3)	71 (15.3)	
T4/N1/M1	36 (2.3)	47 (10.1)	
Unknown/other (TURP detected)	149 (9.3)	88/29 (19.0)/(6.2)	
Biopsy			
Gleason score* *n* (%)			
<7	1111 (69.6)	153 (41.0)	$p < 0.0001$
=7	378 (23.7)	126 (33.8)	
>7	102 (6.4)	93 (5.2)	
Total	1591 (100)	373 (100)	
Unknown	5	45	

* Does not include TURP and cystoprostatectomy in the control arm (*n* = 54).

Table 2 – Therapy choices of patients from the screening and control arm

	Screening arm *n* (%)	Control arm *n* (%)	*p*-Value
Radical prostatectomy	595 (37.3)	84 (18.1)	$p < 0.0001$
Radiotherapy	713* (44.7)	171* (36.9)	
Watchful waiting	231 (14.5)	63 (13.6)	
Endocrine therapy	33 (2.1)	71 (15.3)	
Other	1 (0.1)	2 (0.4)	
Unknown	23 (1.4)	73 (15.7)	
Total	1596 (100)	464 (100)	

* One patient in both screening and control arm received palliative treatment.

Table 3 – Tumour characteristics of radical prostatectomy specimens

Radical prostatectomy Gleason score *n* (%)	Screening arm *n* (%) *n* = 595	Control arm *n* (%) *n* = 84	*p*-Value
<7	355 (46.5)	37 (45.7)	$p = 0.001$
=7	182 (32.4)	34 (42.0)	
>7	24 (4.3)	10 (12.3)	
Total	561 (100)	81 (100)	
Unknown	34	3	
Pathological tumour stage *n* (%)			
pT2#	438 (77.4)	53 (65.4)	$p = 0.07$
pT3a/pT3b	93 (16.4)	19 (23.5)	
pT3c	11 (1.9)	5 (6.8)	
pT4/N1	24 (4.2)	4 (4.9)	
Unknown	29	3	

cancer in 3 and 7 patients in the screening and control arm, respectively. Apart from advanced disease diagnosed by clinical examination (36 in the screening arm and 47 in the control arm), an additional 24 and 4 patients in the screening and control arm were diagnosed pathologically with stage T4 disease (invasion of the bladder wall), lymph node-or distant metastases. The total number of patients with advanced disease was 60 in the screening and 51 in the control arm (6.0 vs. 4.6 per 100,000 man years). The proportion of advanced disease (pathological (pT) stage T4/N1) in RP was only slightly higher in the control arm (4.9 vs. 4.2%).

In RP of the control arm 53.5% of the cancers were Gleason score ≥7, a significantly higher proportion as compared to the 34.6% of cancers in the screening arm (Table 3). Median tumour volumes determined in 40 RP in the control arm were significantly larger (3.9 ml) compared to those found in RP of the screening arm (1.0 ml)

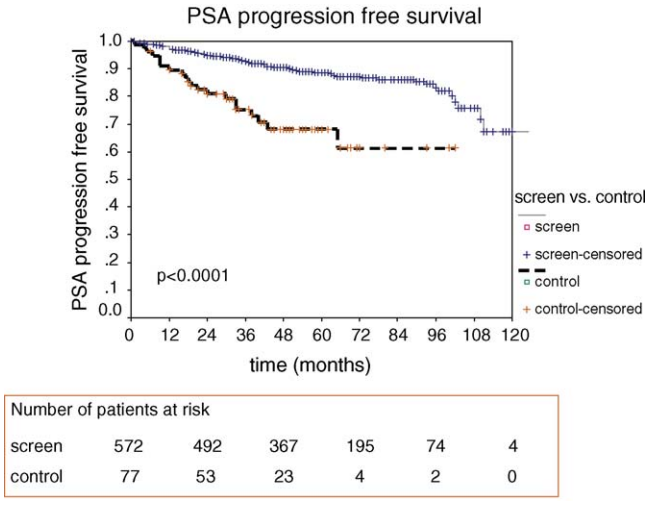

Fig. 1 – PSA progression free survival screen versus control arm after radical prostatectomy.

($p < 0.0001$). Of 27.0% of the RP of men of the screening arm the prostate cancers were stage pT2, Gleason score 6 with a volume <0.5 ml as compared to 11.4% of those of the control arm ($p < 0.01$).

TURP specimens with pT1a cancer and the cystoprostatectomy specimens with cancer (except one) were Gleason score 6 or lower. The cancers found in the cystoprostatectomy specimens as well as the prostatectomies performed according to Millen for BPH were organ confined.

3.4. *Follow up*

Follow up data in the screening and control arm were known for 97% and 93% of patients who underwent RP. Median follow-up after RP or prostate cancer diagnosis in case of TURP or cystoprostatectomy in the screening and control arm was 61 and 42 months, respectively (range 0–126). PSA progression occurred in 71 resp. 21 patients (12 and 25%) and distant metastasis in 3 resp. 6 patients (3.8% and 1.1%) of patients in the screening and control arm after RP, respectively. The 5-year PSA progression free survival was 89 and 68% in the screening and control arm, respectively (log rank $p < 0.0001$) (Fig. 1). However, a log rank test from randomization date to PSA progression showed no statistically significant difference ($p = 0.13$). Three patients with an incidental diagnosis of prostate cancer (1 pT1a, and 2 pT1b), developed metastatic disease. One of 8 patients who underwent a cystoprostatectomy developed PSA progression.

4. Discussion

The significantly higher prostate cancer detection rate in the screening arm (15.9 per 1000 man years) as compared to the control arm (4.2 per 1000 men years) is associated with a shift in clinical stage

and Gleason score distribution of detected cancers. Our data of the diagnostic samples (needle biopsies, TURP) of both arms of the trial now provide direct evidence that the cancers detected in the screening arm have more favourable characteristics as compared to those in the control arm. A similar stage and grade shift during subsequent screening rounds for prostate cancer screening was previously reported by different ERSPC centres [11–13]. Indeed, the difference in prognostic factors between screening and control arm seems to increase further with subsequent screening rounds. In the 1st screening round the proportion of men with a lymph node metastasis was 1.7% of all cancers detected, whereas in the 2nd round this was reduced to 0.2% (data not shown).

The observation of more favourable tumour characteristics in the screening arm as compared to the control arm was also shown in the radical prostatectomy specimens, although treatment bias may have reduced the differences. Patients in the control arm showed a significantly reduced PSA progression free survival after radical prostatectomy, as compared to patients treated in the screening arm ($p < 0.0001$). However, when comparing PSA failure rates from randomization date instead of from date of surgery, no statistical significant difference was found ($p = 0.13$). The latter analysis would compensate for lead-time bias (time between screen-detected and clinically detected prostate cancer). Since lead-time bias in our study was calculated to be 10 years (120 months) [14] and the mean time from randomization to prostate cancer diagnosis in this study was 49, respectively 101 months in the screening, respectively control arm, this would imply a lead-time of only 52 months. This shorter lead-time may arise from opportunistic screening and incidentally diagnosed prostate cancers in the control arm. Therefore analyzing the data from randomization date only in part corrects for lead-time bias.

If the control arm would include a large number of patients offered curative treatment for a tumour which if left untreated would be fatal, but not too advanced for therapeutic intervention this could jeopardize the demonstration of a difference in prostate cancer survival between the control and screening arm. Although the proportion of incidental prostate cancers detected in the control arm is rather high (9.3%) they also include advanced cancers (that is: 6 TURP's with a Gleason score >7, 1 patient with pT1a with distant metastasis). Information of opportunistic screening is not yet complete, but more information is underway. In an earlier report on PSA testing in the control arm of the ERSPC until 1997, it was shown that a large proportion of men in the control arm had a PSA test (20.2%) [15]. However, only 6% of that total proportion of men underwent prostate biopsy and finally 3.0% of these men in the control arm were diagnosed with prostate cancer as a consequence of their increased PSA (effective contamination).

The proportion of men with clinically advanced cancers, likely to be beyond reach of curative treatment (T4/N1/M1) was higher in the screening arm compared to the control arm (6.0 vs. 4.6 per 100,000 man years). This difference is not unexpected and can be explained as follows: (1) more prostate cancers are diagnosed in the screening arm, which automatically leads to a more intense search for metastases [2]. More radical prostatectomies are performed in the screening arm, which in Rotterdam and surrounding hospitals is always preceded by a bilateral lymph node dissection for investigation of metastases increasing the chance of detecting (lymph node) metastases. In addition, clinical T-stage of prostate cancer is frequently underestimated, and therefore the pathological stage might increase after radical prostatectomy (28% of tumours staged as cT3 became pT4/N1/M1 after radical prostatectomy). Importantly, about half of the ''asymptomatic'' advanced prostate cancers could be detected by clinical examination (36 of 60).

The pilot trials performed in the area of Rotterdam suggested a reduction of prostatic cancer specific mortality in the screening arm [16]. We cannot confirm this in the current study, since follow-up is short (61 and 42 months in screening and control arm), in contrast to the data of the pilot trials (10 years). I.e. Bill-Axel son et al. [17] showed that in clinically detected prostate cancer there was no difference in incidence of metastases at a 5-year follow-up period between men treated with radical prostatectomy and watchful waiting. In addition, the median time for PSA recurrence after radical prostatectomy in the screening and control arm was 3 and 5 years, respectively. In a previous report it was stated that at biochemical recurrence after radical prostatectomy, the median time to metastasis was 8 years, and from metastasis to death was 5 years [18]. This implies that the mean age of a man diagnosed in our study at the time of prostate cancer death would be 80 or 83, (mean age at radical prostatectomy in screening and control arm is 64 and 65 years of age) and therefore the chance of dying from a competing cause of dead is high and correspondingly, the chance of dying from prostate cancer after treatment with radical prostatectomy would be small.

5. Conclusions

The prostate cancer detection rate in the control arm is significantly lower compared to its rate in the screening arm. Tumours in the screening arm do have more favourable tumour characteristics compared to the control arm, but advanced disease is slightly more frequently detected in the screening arm.

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