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The Patient Journey from Randomization to Detection of Prostate Cancer and Death: Results from ERSPC Rotterdam

Sebastiaan Remmers [a,], Daan Nieboer [a,b], Monique J. Roobol [a], ERSPC Rotterdam Study Group [†]*

[a] *Department of Urology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, The Netherlands;* [b] *Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, The Netherlands*

Article info

Abstract

Background: The ERSPC study has demonstrated that prostate-specific antigen (PSA)-based screening results in a relative increase in diagnosis of (low-risk) prostate cancer (PCa) and a reduction in metastatic disease and PCa mortality.
Objective: To evaluate the burden of PCa among men randomized to active screening compared to those in the control arm in ERSPC Rotterdam.
Design, setting, and participants: We analyzed data for participants in the Dutch section of the ERSPC, including 21 169 men randomized to the screening arm and 21 136 randomized to the control arm. Men in the screening arm were invited for PSA-based screening every 4 yr, and transrectal ultrasound–guided prostate biopsy was recommended for those with PSA $\geq$3.0 ng/ml.
Outcome measurements and statistical analysis: We analyzed detailed follow-up and mortality data up to January 1, 2019, to a maximum of 21 yr, using multistate models.
Results and limitations: At 21 yr, 3046 men (14%) had been diagnosed with non-metastatic PCa and 161 (0.76%) with metastatic PCa in the screening arm. In the control arm, 1698 men (8.0%) had been diagnosed with nonmetastatic PCa and 346 (1.6%) with metastatic PCa. In comparison to the control arm, men in the screening arm were diagnosed with PCa almost 1 yr earlier and if diagnosed with nonmetastatic PCa lived on average for almost 1 yr longer without disease progression. Among those who experienced biochemical recurrence (18–19% after

nonmetastatic PCa), progression to metastatic disease or death was quicker in the control arm: men in the screening arm lived for 7.17 yr without progression, while the progression-free interval was only 1.59 yr for men in the control arm over a 10-yr time period. Among those who experienced metastatic disease, men in both study arms lived for 5 yr over a 10-yr time period.

Conclusions: PCa diagnosis was earlier after study entry for men in the PSA-based screening arm. However, disease progression was not as fast in the screening arm as in the control arm: once men in the control arm experienced biochemical recurrence, progression to metastatic disease or death was 5.6 yr faster than in the screening arm. Our results confirm the ability of early disease detection to reduce suffering and death from PCa at the cost of earlier (and more frequent) treatment-induced reductions in quality of life.

Patient summary: Our study shows that early detection of prostate cancer can reduce suffering and death from this disease. However, screening based on measurement of prostate-specific antigen (PSA) can also result in an earlier treatment-induced reduction in quality of life.

1. Introduction

The European Randomized Study of Screening for Prostate Cancer (ERSPC) has demonstrated that prostate-specific antigen (PSA)-based screening results not only in a relative increase in diagnosis of (low-risk) prostate cancer (PCa) [1–5] but also in relative reductions in biochemical recurrence (BCR) after radical prostatectomy (RP) [6,7], metastatic disease [5,8], and PCa-specific mortality (PCSM) in comparison to men who were not offered active screening [1–5]. These findings show that the burden of the disease for men randomized to active protocolized screening is different to that for men randomized to the control arm who were subject to opportunistic screening practices.

Despite the promising ERSPC results, population-based screening for PCa is seldom applied in Europe and the rest of the world. This is mainly because of the high rate of overdiagnosis with a purely PSA-based screening algorithm, as was applied in the randomized trials that started in the 1990s. Application of a multivariable risk stratification process [9–11] can considerably reduce overdiagnosis and unnecessary testing. For implementation of risk-stratified population-based early detection programs [11,12], it is important to identify the different phases a man encounters from initial screening to (PCa-specific) death. In addition, information on the duration and burden of each of these phases is mandatory for full appreciation of the benefit of introducing a multivariable individually tailored screening program.

One way to take into account all possible phases that a man can encounter between randomization to screening and death (eg, being diagnosed, experiencing progression) is to transform the whole screening-death pathway to a multistate model. This was recently done with data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) taking into account transitions between the healthy, screen-detected PCa, clinical cancer, and death states [13]. However, the PLCO trial has been criticized because the intervention under investigation (PSA-based screening) also occurred at a high rate in the control arm [14,15]. This so-called contamination was low in the Rotterdam section of ERSPC [16], so a comprehensive analysis of the impact of being screened during the journey from randomization to death is possible. We hypothesized that men who were diagnosed in the screening arm experience less progression and live longer without progression in comparison to men in the control arm.

2. Patients and methods

The Dutch arm of the ERSPC has been described previously [17]. In short, 21 209 men (50%) were randomized to the screening arm and invited for PSA-based screening every 4 yr. In cases with PSA ≥3.0 ng/ml, transrectal ultrasound–guided prostate biopsy was recommended. Screening stopped when PCa was diagnosed, further participation was refused, death occurred, or the man reached the age of 74 yr. A total of 21 165 men (50%) were randomized to the control arm, in which no active screening was offered. It should be noted that in comparison to previous ERSPC Rotterdam publications, one man randomized to the screening arm and one man randomized to the control arm were omitted from the analyses here because they withdrew their informed consent. The ERSPC study database (consisting of men in the screening and control arms) is linked regularly to the database of the Dutch Cancer Registry and Statistics Netherlands to identify PCa diagnoses not detected through active screening and new incidences of death.

After diagnosis, tumor characteristics are assessed according to the 1992 TNM (tumor, lymph node, and metastasis)classification. Detailed follow-up information is recorded via bi-annual chart reviews and includes records of PSA measurements after diagnosis, follow-up treatments, and disease progression events. BCR after RP is defined as two consecutive PSA measurements ≥0.2 ng/ml; BCR after radiotherapy (RT) is defined as a PSA measurement at least 2.0 ng/ml higher than the nadir. Metastatic disease is confirmed on imaging (positive lesion on a bone scan, X-ray, computed tomography scan, or magnetic resonance imaging [MRI]) or as a PSA level >100 ng/ml. The cause of death for men with PCa is assessed by a dedicated Cause of Death Committee according to a fixed algorithm [18].

2.1. Statistical analyses

In the current study, we assumed that ERSPC Rotterdam participants can be in any of six different states: healthy (at the time of randomization), PCa without metastatic disease, BCR, metastatic PCa, other-cause mortality, and PCSM (Fig. 1). Note that "healthy" refers to the state in which men do not have PCa and not to men with limited comorbidities. As an example of our methodology, after randomization, a participant can be diagnosed with PCa with or without metastasis, can die without having had a diagnosis of PCa, or can still be alive without ever having had a diagnosis of PCa. For events that occurred at the same follow-up visit, we used the highest level of progression (eg, men diagnosed with metastatic PCa do not enter the "prostate cancer" state and go directly to the "metastatic disease" state after randomization). For men who died on the day of randomization, we added 0.01 yr to the time between randomization and death.

To model the state transitions between randomization and death, we used a multistate survival model [19–21]. We used this methodology to estimate the incidence of all the transitions stratified for study arm. In addition, we estimated the expected length of stay (ELOS) starting from healthy with a maximum of 20 yr and from the later transitions with a maximum of 10 yr to minimize extrapolation. ELOS was calculated as the area under the survival curve. We assumed that each transition only depends on the current state of the patient (ie, Markov assumption).
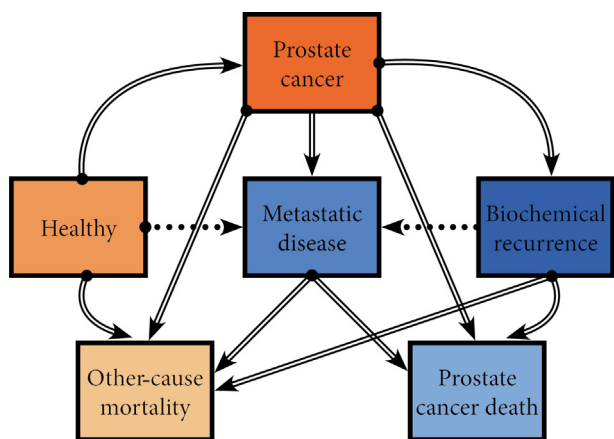
Follow-up time was censored on January 1, 2019, with a maximum of 21 yr. Analyses were performed with R v4.2.1 and the R package *mstate* (R Foundation for Statistical Computing, Vienna, Austria) [22]. We excluded men who had PCa before randomization.

3. Results

We excluded 69 men from the analyses because of PCa diagnosis before randomization. A total of 21 169 men were randomized to the screening arm. During follow-up, 3046 men (14%) were diagnosed with nonmetastatic PCa and 161 (0.76%) with metastatic disease (Table 1). In addition, 9512 men (45%) died without being diagnosed with PCa and 8450 men (40%) were still alive without a PCa diagnosis. A total of 21 136 men were randomized to the control arm. During follow-up, 1698 men (8.0%) were diagnosed with nonmetastatic PCa and 346 (1.6%) with metastatic disease. In addition, 10 199 men (48%) died without being diagnosed with PCa and 8893 men (42%) were still alive without a PCa diagnosis. After a diagnosis of nonmetastatic PCa, 557 men (18%) in the screening arm and 322 (19%) in the control arm experienced progression to BCR; 88 men (2.9%) in the screening arm and 107 (6.3%) in the control arm experienced progression to metastatic PCa without BCR. In addition, after disease progression to BCR, 156 men (28%) in the screening arm and 93 (29%) in the control arm experienced further progression to metastatic disease. In total, 405 patients in the screening arm (1.9%) and 546 in the control arm (2.6%) experienced metastatic disease.

Over a 20-yr time horizon, the average time after randomization without PCa (ie, in the healthy state) was 14.1 yr in the screening arm and 15.0 yr in the control arm (Table 2). Thus, men in the control arm lived on average 0.9 yr longer without a PCa diagnosis or progression than men in the screening arm did. This loss of healthy life years can largely be attributed to early detection of PCa, as men in the screening arm transitioned to the PCa state 0.8 yr earlier than men in the control arm did (0.51 vs 1.32 yr). The loss of healthy life years because of progression to BCR was slightly higher and because of progression to metastatic disease was slightly lower in the screening arm in comparison to the control arm. The loss of healthy life years because of death was comparable between the study arms.

Fig. 1 – Health states for participants in the ERSPC Rotterdam trial.

Table 1 – Number of men experiencing transitions between health states

	Men, *n* (%)						
	PC	BCR	mPC	PC death	OCM	No event	Total
Randomized to the screening arm							
Healthy	3046 (14)	–	161 (0.76)	–	9512 (45)	8450 (40)	21 169
PC	–	557 (18)	88 (2.9)	17 (0.56)	972 (32)	1412 (46)	3,046
BCR	–	–	156 (28)	17 (3.0)	183 (33)	201 (36)	557
mPC	–	–	–	253 (62)	80 (20)	72 (18)	405
PC death	–	–	–	–	–	287 (100)	287
OCM	–	–	–	–	–	10 747 (100)	10 747
Randomized to the control arm							
Healthy	1698 (8.0)	–	346 (1.6)	–	10 199 (48)	8893 (42)	21 136
PC	–	322 (19)	107 (6.3)	16 (0.94)	482 (28)	771 (45)	1698
BCR	–	–	93 (29)	7 (2.2)	87 (27)	135 (42)	322
mPC	–	–	–	319 (58)	93 (17)	134 (25)	546
PC death	–	–	–	–	–	342 (100)	342
OCM	–	–	–	–	–	10 861 (100)	10 861

BCR = biochemical recurrence after radical prostatectomy or radiotherapy; mPC = metastatic PC; OCM = other-cause mortality; PC = prostate cancer.

Table 2 – Expected length of stay in each health state at a horizon of 20 yr after randomization

	Expected length of stay (yr)					
	Healthy	PC	BCR	mPC	PC death	OCM
Randomized to the screening arm	14.14	1.32	0.17	0.05	0.10	4.22
Randomized to the control arm	15.02	0.51	0.08	0.08	0.12	4.20
BCR = biochemical recurrence after radical prostatectomy or radiotherapy; mPC = metastatic PC; OCM = other-cause mortality; PC = prostate cancer.						

Table 3 – Expected length of stay in each health state at a horizon of 10 yr after PC diagnosis

	Expected length of stay (yr)					
	Healthy	PC	BCR	mPC	PC death	OCM
Randomized to the screening arm						
PC	0	7.95	0.91	0.16	0.12	0.87
BCR	0	0	7.17	1.11	0.65	1.08
mPC	0	0	0	4.95	3.91	1.14
PC death	0	0	0	0	10	0
OCM	0	0	0	0	0	10
Randomized to the control arm						
PC	0	7.08	1.05	0.42	0.37	1.08
BCR	0	0	1.59	3.64	3.60	1.17
mPC	0	0	0	5.03	3.40	1.57
PC death	0	0	0	0	10	0
OCM	0	0	0	0	0	10
BCR = biochemical recurrence after radical prostatectomy or radiotherapy; mPC = metastatic PC; OCM = other-cause mortality; PC = prostate cancer.						

Over a 10-yr time horizon, after detection of non-metastatic PCa, men in the screening arm lived on average almost 1 yr longer with PCa without experiencing disease progression or death from any cause in comparison to men in the control arm (7.95 vs 7.08 yr, Table 3). After a PCa diagnosis, progression to BCR was quicker for men in the control arm (0.91 vs 1.05 yr; difference 0.14 yr) than for men in the screening arm, as was progression to metastatic disease (0.16 vs 0.42 yr; difference 0.26 yr). In addition, the time from diagnosis to death (PCSM or other-cause mortality) was shorter in the control arm than in the screening arm. For participants experiencing BCR, progression to metastatic disease or death occurred on average 5.6 yr earlier for those in the control arm. Among the men who experienced BCR, 1.1 yr of living with recurrence were lost because of metastatic disease for those in the screening arm, compared to 3.6 yr for those in the control arm (difference 2.5 yr). In other words, once BCR occurred, progression to metastatic disease was much faster for men not subject to active screening. For men with metastatic disease, either at diagnosis or during follow-up, life expectancy was 5 yr over a 10-yr time horizon.

4. Discussion

In this study we assessed the difference in PCa burden by comparing the incidence and duration of six different health states between men who are actively screened according to a fixed protocol (screening arm) and men who are not screened at all or screened at a low level in an opportunistic setting (control arm). Our data clearly show the impact of overdiagnosis of a purely PSA-based algorithm. We observed that active repeated PSA-based screening resulted in detection of more PCa cases (excess incidence of 636 PCa diagnoses per 10 000 men randomized). Active screening,

which brings PCa diagnosis forward in time, reduced "healthy" life years (ie, without a PCa diagnosis) by 0.9 yr in comparison to the control arm over a 20-yr time period. This implies that men in the screening arm who are diagnosed with PCa will experience a decrease in quality of life (QoL) at an earlier time point (and more often) owing to the primary treatment given for PCa [23–25]. Several QoL domains stabilize over time after treatment, but almost never return to pretreatment levels, as demonstrated by 5-yr follow-up data from the ProtecT trial [24]. These data highlight the importance of active surveillance (AS), as the majority of the excess incidence that occurs because of PSA-based screening (and systematic prostate biopsy) consists of low-risk PCa cases that do not require these life-deteriorating invasive treatment modalities. QoL data for men following AS protocols are promising [26] although it must also be noted that of the first 500 men included in the PRIAS trial, 325 (65%) switched to active treatment within a median of 2.3 yr [27]. This will certainly impact the initial benefit of AS in reducing the harm of overdiagnosis.

We also observed that men with screen-detected PCa live with their PCa without experiencing progression or death for longer on average than men randomized to the control arm (7.95 vs 7.08 yr). The times to progression, metastatic disease, and death for patients with PCa were shorter in the control arm than in the screening arm. However, it should be mentioned that PCa detection was later in the control arm than in the active screening arm. This means that interpretation of our results after diagnosis should take into account the risk of being diagnosed with PCa.

Our previous study showed that men in the screening arm had a lower incidence of BCR after RP [6], while in the current study the incidence of BCR after RP and RT during the follow-up period was similar between the trial arms.

However, for the subgroup of men who opted for RP, we observed results comparable to our previous finding. Importantly, our data show that for men experiencing BCR, progression to metastasis or death was more rapid in the control arm than in the screening arm. For men experiencing BCR, those in the screening arm lived for 5.6 yr longer in the BCR state in comparison to men in the control arm. This implies that men in the control arm who experience BCR will need to switch earlier to treatment modalities for metastatic PCa, which severely affect QoL [23,28]. Our results can be used to inform patients about the harms and benefits of screening for PCa using decision aids. Results for the average time spent in each state can be used to set more comprehensive expectations regarding the long-term benefit of attending screening besides reducing mortality. Once men reached the metastatic state, they lived for 5 yr on average in both study arms, indicating that the gain provided by early detection lies in the possibility of cure. This is in line with earlier work that revealed that the decrease in metastatic disease is the major contributor to the reduction in PCa mortality in ERSPC [29].

It is unlikely that the rates of progression to BCR and to metastatic disease observed can be attributed to different treatment modalities at diagnosis. A study using ERSPC Rotterdam data revealed a small association between the trial arms and primary treatment [30]. A recent update of the ERSPC data with 16-yr follow-up, including data from Finland, The Netherlands, Sweden, and Switzerland, demonstrated that the difference in initial treatment was not related to the reduction in PCSM [31]. Rather, differences in treatments can be attributed to the favorability of tumor characteristics at the time of diagnosis.

It is expected that in Europe, PCa incidence will increase by 26% and PCSM incidence by 55% by 2040 in comparison to 2020 [32]. This high incidence and the potential disease burden highlight a need to identify patients at risk of dying from PCa to maintain their QoL as much as possible, as we have shown that men who undergo screening and are diagnosed with PCa have longer progression-free survival on average than men who do not undergo screening. To reduce the number of aggressive PCa cases requiring aggressive treatment, early detection via an adequate risk stratification methodology to reduce overdiagnosis and implementation of individual risk-adapted AS schemes to reduce overtreatment and unnecessary biopsies are essential to maximize the benefit of PCa screening. A European Association of Urology position paper on early detection of PCa recommends risk stratification for men with elevated PSA to identify those who are most likely to benefit from MRI [11]. In the final step, MRI results can guide referral for prostate biopsy.

The main limitation of our study is that the data are from a single center. However, the reported effect of PSA-based screening in ERSPC Rotterdam in reducing metastatic disease [8] and PCSM [4] is consistent in comparison to overall data from ERSPC as a whole. In addition, we did not stratify our results by initial and secondary treatments or by tumor characteristics as this would lead to subgroups too small for meaningful analysis.

Strengths of our study include the limited nonattendance in the screening arm and limited contamination in the control arm. Kerkhof et al. [16] identified a nonattendance rate of 6% in the screening arm and a contamination rate of 12% in the control arm. This allows us to draw conclusions regarding the impact of PCa screening practices. Another strength is the presence of prolonged and detailed follow-up (data have been collected from 1993 onwards) and a dedicated Cause of Death committee that classifies the cause of death for patients with PCa using detailed information from clinical records according to a standardized protocol [18].

5. Conclusions

In conclusion, our detailed and prolonged follow-up provides insight into the phases men can encounter between randomization and death after PSA-based screening. We observed that men who underwent screening lived on average 0.9 yr less in the healthy state (14.1 vs 15.0 yr) in comparison to men in the control arm, a time window during which men have to live with lower QoL. By contrast, in a non-screening setting more men will encounter the highly burdensome phase of metastatic disease, either at the time of diagnosis or due to progression after an initial diagnosis of nonmetastatic PCa. Starting from the BCR state, average time to progression to metastatic disease or death was 5.6 yr earlier for men in the control arm. In particular, the metastatic state has an enormous impact on QoL. Implementation of individual risk–based screening at a European level should be discussed again in light of these data and the (expected) burden of PCa.

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