Screening for Prostate Cancer

Intermediate Outcome Measures and Active Surveillance

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Screening for Prostate Cancer
Intermediate Outcome Measures and Active Surveillance

Vroegopsporing van prostaatkanker
Intermediaire eindpunten en actief afwachtend beleid

Proefschrift

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The process of scientific discovery is, in effect, a continual flight from wonder

Albert Einstein

Voor mijn ouders

Contents

PART I

GENERAL INTRODUCTION

Chapter 1

History

The prostate was first described by Niccolò Massa in 1536, and illustrated by Andreas Vesalius in 1538. However, prostate cancer was not identified until 1853 by J. Adams, a surgeon at The London Hospital.[1] He noted in his report that this condition was 'a very rare disease'. The first treatment modality for prostate cancer was surgery to relieve urinary obstruction.[2] Removal of the entire gland (radical perineal prostatectomy) was first performed in 1904 by Hugh Young at Johns Hopkins Hospital.[3] The operation involved removal of the entire prostate gland, the seminal vesicles, and a small cuff of bladder, with the bladder then sutured to the cut end of the urethra. This became the surgery of choice until the 1940s. By that time, prostate cancer was increasingly being detected and the typical patient was a man in his early seventies who was diagnosed with metastases to the bone and/or soft tissues. Diagnosis at such an advanced disease status was a death sentence, with patients dying within 1–2 years. In 1941 Charles B. Huggins (figure 1.1) discovered that metastatic prostate cancer responds to androgen-ablation therapy through orchiectomy, which heralded the beginning of a new era of prostate cancer therapy.[4] The discovery of 'chemical castration' won Huggins the 1966 Nobel Prize in Medicine.

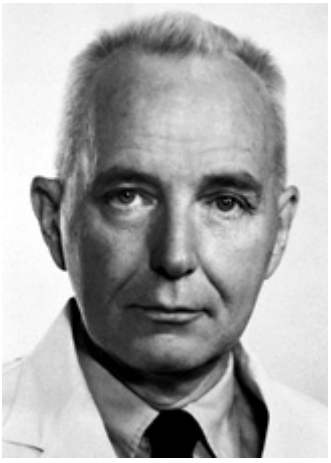

Figure 1.1 Charles B. Huggins

The next surgical advance came in 1945 when Terrence Millin introduced the retropubic approach for prostate enucleation.[5] This approach offered significant advantage over the perineal approach because it was easier to learn and allowed access to the pelvic lymph nodes, which is useful for tumor staging. Although minor improvements in technique were made over the next 40 years, prostatectomy was not commonly performed because almost all patients were left impotent by the procedure. A significant advance occurred in 1983 when Patrick Walsh (figure 1.2) developed a modified technique for radical retropubic prostatectomy on the basis of an anatomical approach to enhance control of bleeding. This approach aims to avoid injury to the neurovascular bundles that innervate the corpora cavernosa of the penis, thereby

Figure 1.2 Patrick C. Walsh

allowing erectile function and sexual potency to be maintained without compromising the adequacy of surgical margins.[6]

External beam radiotherapy was initially used only as an adjunct to interstitial radium because the kilovoltage delivery systems were not adequate to allow definitive treatment of most deep-seated neoplasms such as prostate cancer. With the discovery of androgen-ablation therapy in the early 1940s, radiation therapy lost popularity as a treatment modality for prostate cancer. Renewed interest in radiation therapy returned in the 1950s when higher-energy cobalt machines were developed, whose photon beams could penetrate to deeper levels. The first reported series of prostate cancer patients who were treated with 60Co(cobalt) therapy focused on patients with unresectable disease.[7] Soon after, Juan Del Regato reported on a small number of patients who were apparently cured following 60Co-therapy.[8] In the late 1950s, pioneering work by Malcolm Bagshaw and others revealed the possibility of radiation curability of prostate cancer.[9,10] The past decade has witnessed widespread acceptance and use of prostate brachytherapy. Interest in the procedure first appeared almost 90 years ago, and noted clinicians performed hundreds of implants in the first quarter of the 20th century.[11]

Chapter 2

Introduction

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Fritz H. Schröder

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SCREENING FOR PROSTATE CANCER

Rationale of screening

Screening for diseases, especially cancer, has become part of modern medicine. Screening for breast, cervical and colorectal cancer is already normal practice in some countries, and will probably become routine in other countries in the future.[12-16] Screening for malignant melanoma, prostate and lung cancer are subject to ongoing studies.[17-20] The rationale behind screening is simple: to detect cancers at an early stage, when they are still curable. Screening is currently performed using one of three methods: mass screening (i.e. large scale screening of an entire population), selective screening (i.e. screening high-risk populations) or opportunistic screening (e.g. incorporated as part of a medical consultation). Diagnostic testing differs from screening because it attempts to identify the disease in the presence of symptoms, while screening is offered to symptom-free individuals.

In any population screened for cancer, however, four basic groups of patients exist: Those diagnosed with cancer who would not have developed cancer symptoms during their lifetime (overdiagnosis). Those diagnosed with cancer at an early stage that might otherwise have led to symptoms and/or the need for more aggressive curative treatment. Those diagnosed with cancer at a curable stage with aggressive disease that might otherwise have progressed to metastatic disease at the time of diagnosis; and those whose cancer is diagnosed by screening at the same stage as it would have been diagnosed through clinical routines. The window of opportunity for decreasing cancer-mortality by screening for cancer lies with the third group. Randomized clinical trials, considered the gold standard for the evaluation of a screening test, have to show how sizeable that window is.

European Randomized study of Screening for Prostate Cancer (ERSPC)

At present, two large randomized screening trials for prostate cancer are underway: the ERSPC in Europe, and the Prostate, Lung, Colorectal and Ovary cancer (PLCO) trial in the US.[18] The ERSPC has recruited more than 250,000 men in eight European countries, in order to determine whether the price of reducing prostate cancer mortality through population-based screening is acceptable in terms of quality-of-life consequences and costs.[21] The answer, based on trial evidence, will not be available before 2008-2010.

Prostate specific antigen (PSA)

PSA is a glycoprotein manufactured almost exclusively by the prostate gland. It is a serine protease enzyme, the gene of which is located on the nineteenth chromosome (19q13).[22] Increased levels of PSA may suggest the presence of prostate cancer. However, prostate cancer can also be present in the complete absence of an elevated PSA level.[23]

Prostate cancer incidence

Since the potential value of PSA for the early detection of prostate cancer was described in the early 1990s, both prostate cancer incidence and mortality rates have changed profoundly (figure 2.1).[24] Between 1989 and 2003, for example, the age-standardized incidence rate of prostate cancer increased by 48.4% in The Netherlands, reaching an incidence of 93.2 cases per 100,000 men or 7,902 in total. Based on rates from 2001-2003, 17.1% of U.S. men born today will be diagnosed with cancer of the prostate at some time during their lifetime.[25] It is now the most frequently diagnosed non-cutaneous cancer with 225,000 new cases reported each year in Europe alone.[26] Moreover, autopsy studies have revealed that prostate cancer occurs in an even larger proportion of men: 55% of men in their fifties, and 64% of men in their seventies.[27] If the current trends toward using lower PSA thresholds to determine the need for biopsy, and taking more core samples per biopsy continues, the number of living men diagnosed with prostate cancer will increase even further.[28-30] Based on the data from the control arm of the Prostate Cancer Prevention Trial (PCPT) it can be calculated that if all U.S. men with PSA levels 2.5 ng/mL or more 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.[23,30,31]

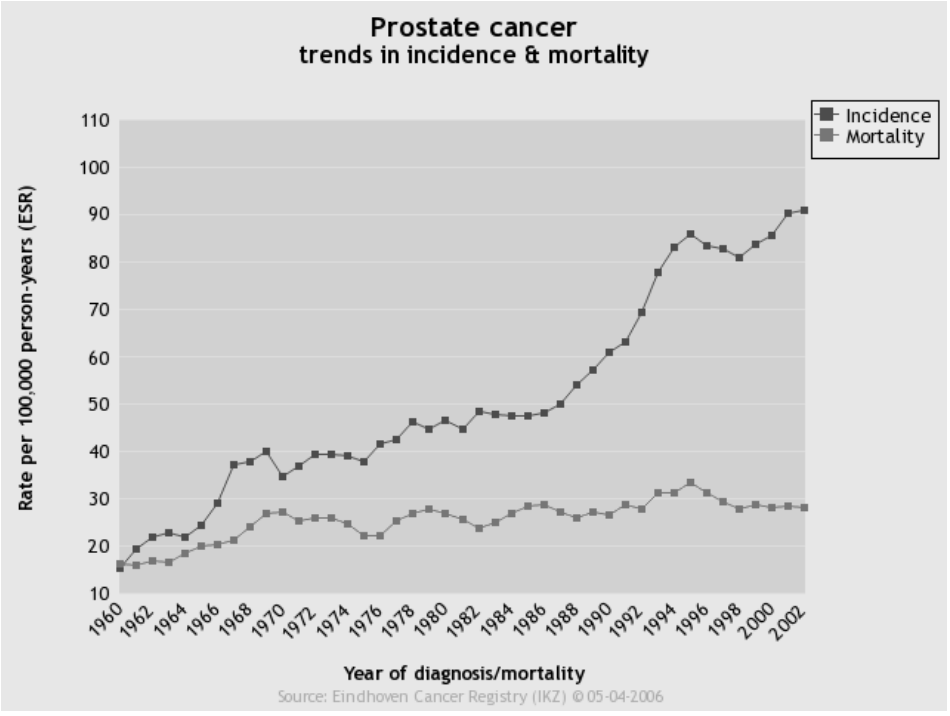

Figure 2.1. Prostate cancer incidence and mortality trends in the Netherlands.

Prostate cancer mortality

Despite this rising incidence, the age-standardized prostate cancer mortality rate in The Netherlands fell by 11% between 1989 and 2003, to 28.4 deaths per 100,000 men or 2,349 in total.[32] Whether this decrease is the result of screening or of improvements in treatment is controversial. Currently, one in four deaths in the United States is due to cancer. Of those, 9.4% is due to prostate cancer, which makes it the most important cause of death in males after lung cancer and colorectal cancer with an expected number of 27,350 deaths in 2006.[33]

Screening and stage migration

Screening results in the more frequent detection of small volume, low grade and organ confined prostate cancers, which are diagnosed earlier in their course.[24] It is however unclear whether the stage and grade migration results in a reduction in the mortality, although case-control studies with conflicting results are available.[34-36] Lead time is defined as the time period from screening detection to diagnosis in absence of screening. If the patient dies during the lead-time period of the tumor, the lead-time is indefinite and therefore equal to overdiagnosis.

Overdiagnosis

Overdiagnosis occurs when screening detects small tumors that would otherwise remain clinically unrecognized until the individual died from other causes. It is not known whether the shift towards diagnosis of aggressive cancers at a favorable stage justifies the amount of overdiagnosis and the costs associated with screening.

The impact of overdiagnosis and unnecessary treatment and of its side effects on patient health is also unclear; however, application of a mathematical model (the Miscan model) on data from the ERSPC has shown that, in an annual screening program for men aged 55 to 67 years, 56% of diagnosed cases would constitute instances of overdiagnosis.[37] If this estimate proves to be realistic, nationwide screening programs may not be acceptable using the present screening regimens, even if benefits in terms of mortality reduction were shown. Research aimed at the development of more selective screening tools is therefore very important.

Morbidity

Although the risk of complications from an individual prostate biopsy is very small,[38] the cumulative risk posed by repeated prostate biopsies in a large population could become quantitatively important, specifically for overdiagnosed cases. Furthermore, besides the medical consequences of screening tests, the emotional consequences of screened men must also be considered.

Quality of life

Research suggests that, overall, other than during the short period related to the screening process and to the biopsy procedure, screening does not adversely influence patients' short-term health.[39] Indeed, many men report feeling reassured as a result of screening, especially after receiving a 'normal' result. However, a diagnosis of prostate cancer, which occurs more frequently in a screening setting (i.e. overdiagnosis), has a negative influence on the quality of life.[40]

It is still too soon to say whether population-based prostate cancer screening is a useful tool. We must wait until the results of ongoing prostate cancer screening trials are available. Until then, opportunistic screening should not be encouraged and those men who do want a PSA test should participate in a carefully designed, balanced information program.[41] Even if PSA screening is found to reduce prostate cancer-specific mortality, levels of overdiagnosis may remain unacceptable for population based screening. Thus, research into mechanisms to reduce overdiagnosis including new markers is urgently needed. Until alternative screening tools are found, PSA will continue to be used, and overdiagnosis will remain an unavoidable drawback of prostate cancer screening. The current challenge is to ensure that overdiagnosis does not result in overtreatment. To this end, research efforts presently focus on clarifying which cancers can be managed through active surveillance.

ACTIVE SURVEILLANCE

Ways out of the dilemma of overtreatment

Because not all cancers diagnosed require treatment, one of the major challenges for the future is to determine which diagnosed cancers should be treated, and which can be managed by active surveillance. Active surveillance manages selected men with prostate cancer expectantly with curative intent. This means men are carefully selected and subsequently actively observed in order to have the possibility to offer them deferred curative treatment once the tumor seems to progress. Active surveillance should be clearly differentiated from watchful waiting. 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 tumor becomes progressive and curative treatment can be offered. The stage migration that screening provides has resulted in an over-representation of low-risk cancers. Therefore, studies which validate monitoring algorithms in active surveillance regimens are ongoing.[42,43]

Arguments to elect active surveillance include the prevention of overtreatment, the side-effects of prostate cancer treatment modalities, quality of life issues, costs associated with treatment and ethical arguments.

Overtreatment

The increasing use of PSA as a screening test due to a higher awareness of the disease, the increasing number of biopsies, the increasing number of cores per biopsy and the increasing life expectancy have resulted in a more frequent diagnosis of prostate cancers, which are of lower grade and stage.[44-46] The majority of these (screen-detected) prostate cancers have a good long-term survival, especially when only a small number of cores with well-differentiated prostate cancer was diagnosed.[47,48] Screening diagnoses prostate cancers which would not have been diagnosed in the absence of screening (i.e. overdiagnosis).[48] As mentioned above, the amount of overdiagnosis is subject to investigation. Etzioni et al. applied a computer model to the SEER data on prostate cancer incidence from 1988 through 1998. Those were consistent with overdiagnosis rates of approximately 29% for whites and 44% for blacks among men with prostate cancers detected by PSA screening.[48] With the increasing screening use of PSA, it is remarkable that the amount of U.S. men initially managed with watchful waiting increased from 7.5% in 1989 to 1991 to 9.5% in 1992 to 1994, and then decreased significantly during the next 6 years to 5.5% in 1998 to 2000.[49]

Side effects of treatment

Treatment for prostate cancer may involve surgery, external beam radiation therapy, brachytherapy, high intensity focused ultrasound (HIFU), watchful waiting, active surveillance, chemotherapy, cryosurgery, hormonal therapy, or combinations. The most frequently applied treatments for organ confined prostate cancer are radical prostatectomy, external beam radiotherapy and brachytherapy.[49]

Although severe or life-threatening complications with radical prostatectomy are rare, the adverse effects of greatest concern are damage to the urinary sphincter and erectile nerves (nervi erigenti), resulting in urinary incontinence and impotence, respectively. Complete incontinence is uncommon after radical prostatectomy, although a significant number of men experience some degree of stress urinary incontinence.[50-52] In the Prostate Cancer Outcomes Study, a population-based study of 1,291 men who underwent radical prostatectomy for localized prostate cancer and were followed for two years, 1.6 percent reported no urinary control at 24 months following surgery (compared with 0.7 percent at baseline prior to surgery), while 7 and 42 percent reported frequent and occasional leakage, respectively (compared with 2 and 9 percent at baseline).[51] Age had an impact on the degree of incontinence; 14 percent of men ages 75 to 79 years experienced the highest level of incontinence compared with 0.7 to 4 percent of younger men. In the Prostate Cancer Outcomes Study, 42 percent of men reported that sexual performance was a moderate to large problem at 24 months (compared with 18 percent at baseline); 60 percent were not able to have erections firm enough for sexual intercourse (compared with 16 percent at baseline).[51] At 24 months postoperatively, men over the age of 60 were more likely to be impotent than younger men (78 to 85 versus 61 percent).

Complications after external beam radiotherapy include bladder irritation (urgency, pain, frequency) in up to 5 percent of men, and impotence in 40 to 50 percent.[53] In contrast to surgery, these complications tend to increase over time. The reported incidence of radiation proctitis ranges from 2 to 39 percent, depending upon the definition used, and the dose field, and technique of radiotherapy. Prostate inflammation and swelling can occur acutely following brachytherapy, suggesting that men with significant urinary symptoms or a large prostate are not good candidates. Urinary retention can be severe enough to require self-catheterization; transurethral resection to improve micturition is contraindicated until a substantial portion of the radioactivity (usually 5 half-lives) has dissipated because of the risk of incontinence and radiation risks to the surgeon and pathologist. Later complications include irritative voiding symptoms, urinary retention, rectal urgency, bowel frequency, rectal bleeding or ulceration, and prostatorectal fistulas.[54-56] The incidence of erectile dysfunction ranges from 14 to 52 percent, depending on whether it is physician- or patient-reported.

Quality of life

The more immediate, though stable, side effects associated with surgery should be weighed against the increasing incidence of symptoms and use of treatments after the progression of disease in active surveillance.[57] Published empirical studies on prostate cancer specific and generic health related quality of life (HRQoL) in patients on active surveillance of localized prostate cancer are scarce. Many studies have a cross-sectional design resulting in limited comparability largely due to uncertainty about the selection of patients and seemingly contradictory results. Still the evidence supports hypotheses that being on active surveillance causes uncertainty and distress and may have negative effects on generic HRQoL.[58] In the series reported by Choo, 14 out of 69 men who discontinued the active surveillance protocol did so without signs of disease progression. The benefit of prevention of side effects of active therapy must be weighed against the impact of anxiety and uncertainty in patients on active surveillance.[59,60]

In a study among 326 participants randomized to either radical prostatectomy or watchful waiting, mental health and overall well-being were similar in both groups after a median follow-up of 4 years.[61] The CaPSURE study showed that mental health remained stable over time among watchful waiting patients, but that physical scores and sexual function decreased more than expected from the aging process alone.[62] Mental scores were slightly worse compared to radical prostatectomy patients, but better than patients who underwent radiotherapy.[63] In men receiving no active treatment satisfaction was less than in actively treated men.[64]

Steginga found moderate distress around diagnosis in a prospective study among patients undergoing prostatectomy, radiotherapy or watchful waiting, which decreased afterwards. 42% of men still experienced decision-related distress after 12 months.[65] In a review on anxiety

in prostate cancer, Dale concluded that many years after initial therapy, high anxiety levels were less prevalent after prostatectomy (23%) than in watchful waiting (31%).[66] Daubenmier evaluated the effect of a lifestyle intervention among men on active surveillance. Generic HRQoL remained high in the intervention group. Men in the intervention group perceived less stress, suggesting that diet, exercise and stress management is beneficial in men on active surveillance.[67] In men receiving no active treatment, satisfaction was less than in actively treated men.[64]

One as yet unpublished Dutch population-based study among long term survivors of prostate cancer showed comparable generic HRQoL scores among patients who underwent radiotherapy or watchful waiting, with patients after prostatectomy showing better scores. However, the choice of watchful waiting seemed to be the policy for very old patients.[68] Knowledge of the mechanisms behind treatment choices in localized prostate cancer is limited. Knowledge and understanding of prostate cancer and of the uncertainty of benefit from active treatment, as well as active support from medical professionals, seems pivotal for patients to consider active surveillance.[69] Fear of future consequences of progressive prostate cancer may be the most common reason to reject active surveillance.[70] A study on patient education needs of men on active surveillance is ongoing at the University of California in San Francisco.

Costs

Another argument for active surveillance is the costs of treatment. Although no literature is available, it seems rational that active surveillance is less expensive than immediate treatment. An unpublished study originating from Erasmus MC has revealed that the cost-savings for a system which has incorporated active surveillance as an important treatment modality are substantial. This analysis takes into account the medical consequences from treatment, but leaves social and quality of life consequences out of consideration.

Ethical aspect

The most important argument for active surveillance is probably an ethical one: one can wonder what number needed-to-treat to prevent one prostate cancer death our profession is prepared to accept. Based on the Swedish randomized trial of radical prostatectomy versus watchful waiting, the Connecticut observation series, and the Toronto active surveillance experience, an analysis of the benefit of radical treatment of all newly diagnosed favorable-risk prostate cancer patients, compared with a strategy of active surveillance with selective delayed intervention, has been presented by Klotz.[71] This number needed to treat analysis suggests that approximately 73 patients will require radical treatment for each prostate cancer death averted. This translates into a 3- to 4-week survival benefit, unadjusted for quality of life. If any, the number of life-years gained can be expected to be small, also because prostate cancer is a disease of older age. This should be contrasted to the side-effects of all applied

treatments. As a minimum, the number of men needed to treat should be higher than the number of men dying from intervention related causes.

Chapter 3

Scope

The introduction of the PSA test and its use as a screening test have led to a marked increase in the number of newly diagnosed prostate cancers in countries where screening is prevalent.[24,25,72,73] Whether screening affects prostate cancer mortality is still unclear, but is the main research question for the ERSPC and the PLCO to answer.[18] Whatever these trials conclude, it is likely that opportunistic PSA screening will continue to be used for screening, although a positive effect of screening on the mortality will make a population based screening program more likely. The performance of the PSA test together with the high incidence-to-mortality ratio and the high prevalence of the disease in older men have confronted the medical community and especially the urological world with new dilemmas. Basic research endeavors have led to the discovery of new, more specific markers for prostate cancers, but not to a new standard for the detection of prostate cancer which offer the possibility for risk stratification.[74,75]

Until new predictors for the detection of only the significant prostate cancers become available, the high incidence, the serious side effects of prostate cancer treatments, the costs and especially ethical aspects oblige us to cope with the side-effects of screening for prostate cancer, such as overdiagnosis. This thesis focuses on one way out of the PSA screening dilemma described above, namely active surveillance. It would be preferential to prevent the detection of insignificant cancers, but that is for the present impossible and is beyond the scope of this thesis. For this thesis, a situation is therefore accepted in which men are diagnosed with insignificant prostate cancer. It is further explored what kind of cancers are diagnosed by screening, how to subsequently risk-stratify them and what the best strategy is for active surveillance of a subset of these cancers.

PART II

EFFECTS OF SCREENING FOR PROSTATE CANCER

Chapter 4
Biochemical progression rates in the screen arm compared to the control arm of the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC)
Prostate. 2006 Jul 1;66(10):1076-81

Chapter 5
Overall survival in the intervention arm of a randomized controlled screening trial for prostate cancer compared to that in a non-screened cohort
Eur Urol. 2007 Jun 12; [Epub ahead of print]

Chapter 6
Feasibility study of adjustment for contamination and non-compliance in a prostate cancer screening trial
Prostate. 2007 Jul 1;67(10):1053-60

Chapter 4

Biochemical progression rates in the screen arm compared to the control arm of the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC)

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Prostate. 2006 May 1;66(6):625-31

ABSTRACT

Introduction

The European Randomized study of Screening for Prostate Cancer (ERSPC) investigates the feasibility of population-based screening. This report compares the preliminary outcome of cancers detected in the screen and the control arm of its Rotterdam section, by means of biochemical progression rates.

Patients & Methods

In the screen arm of this study (21,210 men), screening was applied according to well-established protocols, and a 4-year screen interval was chosen. Widely accepted biochemical progression-criteria were used to evaluate the diagnosed cancers over time.

Results

Although more cancers were detected in the screen than in the control arm (1,339 vs. 298, $P<0.001$), their clinico-pathological features were more favorable. Furthermore, screened men had higher 5-year survival rates for biochemical progression after surgery (84.4% vs. 58.9% in controls), radiotherapy (71.0% vs. 58.0%), and endocrine therapy (40.5% vs. 16.3%).

Conclusion

The higher biochemical progression-free survival can at least in part be explained by lead and length-time. How screening will affect the mortality remains unclear.

INTRODUCTION

Since prostate-specific antigen (PSA) screening for prostate cancer became available in the late 1980s,[24] both prostate cancer incidence and mortality rates have changed profoundly. Between 1989 and 2002, for example, the age standardized incidence rate of prostate cancer increased by 38.7% in the Netherlands (reaching 87.1/100,000) and by 21.3% in the United States (reaching 176.3/ 100,000).[32,73] It is now the most frequently diagnosed non-cutaneous cancer, with 225,000 new cases occurring each year in Europe alone.[26] Between 1989 and 2002 in the Netherlands, however, the age standardized prostate cancer mortality rate fell by 8.5% to 29.2/100,000,while in the USA it fell by 17.6% to 28.1/100,000 during the same period.[32,73] Whether this decrease is the result of screening or of improvements in the therapy administered is still a matter of debate. At present, two large randomized clinical screening trials for prostate cancer are ongoing: The European Randomized study of Screening for Prostate Cancer (ERSPC) in Europe, and the Prostate Lung Colorectal and Ovary cancer (PLCO) trial in the USA.[18] The first of these (the ERSPC) has recruited and randomized approximately 250,000 men in eight European countries in order to determine the feasibility of reducing prostate cancer mortality through population-based screening, and whether this is acceptable in terms of quality of life and cost.[76] Although prostate cancer screening leads to the diagnosis of men with smaller volume,[77] lower grade, earlier stage tumors,[49] it also results in overdiagnosis and overtreatment. The results of screening studies are subject to lead-time bias and length-time bias. Lead-time is the time period from screen diagnosis to the moment the patient would have developed symptoms in the absence of screening. The associated overdiagnosis, which is inherent to screening, is defined as the detection of small tumors that would otherwise remain clinically covert until the patient died from other causes. Overdiagnosis by definition occurs when the lead-time is larger than the life expectancy. Length time bias is introduced by screening because it detects many indolent cancers, with a slow natural course, which would have remained subclinical in a non-screened population. Whether the down-staging of tumors, with the expected survival benefit, is balanced by the created overdiagnosis with its consequences has to be evidenced by studies such as the PLCO and/or the ERSPC. Although the definitive results of the ERSPC are not expected before 2008, this report provides biochemical progression parameters from the Rotterdam section of the ERSPC.

PATIENTS & METHODS

Between November 1993 and January 2000, a total of 42,376 men, aged 55–74, were randomized in the Rotterdam section of the ERSPC. The conditions and algorithm of the ERSPC are described in greater detail elsewhere.[78] In short, of 21,210 men randomized to the screen arm, 19,970 (94.2%) were actually screened. From November 1993 through May 1997 all men

with suspect findings on digital rectal examination and/or trans-rectal ultrasound and all men with a PSA ≤ 4.0 ng/mL were biopsied. Later on, digital rectal examination and trans-rectal ultrasound were omitted as an indication for sextant biopsy and the PSA-threshold value for biopsy was lowered to 3.0 ng/mL. All men in the screen arm who were still eligible for screening after 4 years were reinvited for repeat screening. The 21,166 men in the control arm of the ERSPC received standard medical care, which meant that the evaluation of symptoms, a diagnosis of prostate cancer and subsequent treatment, or refrainment from it, was provided by general practitioners and local urologists. Men with prostate cancer in the control arm were identified through a linkage with the Comprehensive Cancer Registry (CCR).[79] For this report, the cut-off date for diagnosed prostate cancers was January 2001 in both the screen and the control arm.

Follow-Up

Follow-up data were obtained by reviewing patients' charts every 6 months for the first 5 years following diagnosis and annually thereafter. Medical history, physical examination, dissemination studies, and PSA tests were registered. Endpoint in this study was PSA-progression. This was defined as two consecutive PSA values of 0.2 ng/mL or higher after radical prostatectomy; three consecutive PSA increases meant progression after radiotherapy, following the criteria of the American Society for Therapeutic Radiology and Oncology (ASTRO-criteria).[80] The time of PSA progression was backdated to the date between the first rise and the previous PSA test-date. The criteria described by Collette et al. were used for PSA progression in men with metastatic disease receiving endocrine treatment (e.g. a first PSA increase of 20% over nadir, each to a value>4.0 ng/mL).[81] Clinical staging is done throughout the whole study according to the 1992 UICC TNM classification.[82] No progression rates were calculated for watchful waiting because no widely accepted definition for disease progression exists and most watchful waiters will receive treatment once their PSA values increase too rapidly.

Histology

Sextant biopsy was performed as described by Eskew et al.[83] Biopsy Gleason scores of all screen-detected prostate cancers were provided by a single genito-urinary pathologist.[84] After the identification of men with prostate cancer in the control group, the histological slides with prostate cancer were retrieved from the pathologic storage facilities of all hospitals, and the Gleason scores were reviewed for all cases.

Statistics

All statistical tests were performed using the Statistical Package for the Social Sciences (SPSS version 12.0.1; SPSS incorporated, Chicago, IL). Statistical significance was defined as a P-value <0.05.

RESULTS

From the start of this screening study (1993) to the end of the year 1999, 1,339 of 19,970 (6.7%) men screened were diagnosed with prostate cancer in the screen arm. Of those, 1,014 were diagnosed in the prevalence screen (i.e., the first round). In the control arm 298 men (1.4% of 21,202) were diagnosed. The number of cancers per 1,000 randomized men was 67.1 for the screen arm and 14.1 for the control arm (P-value <0.0001). Interval carcinomas are those tumors that are clinically detected in between the screen rounds. During the 4-year screen interval in our study 54 of those carcinomas were detected. As table 4.1 shows, screened men have a lower age at diagnosis (67.0 vs. 69.0 years, P-value <0.0001), have lower biopsy Gleason-scores and they have lower PSA levels at the time of diagnosis (median 5.5 ng/mL vs. 11.7 ng/mL, P<0.0001). The clinical T-stage in the screen group was more favorable, and less nodular metastases (1.5% vs. 4.0%, P<0.0001) and distant metastases (1.0% vs. 8.7%, P<0.0001) at diagnosis were found. In the control arm, significantly more men were treated with endocrine therapy as their initial therapy (3.0% vs. 20.1%, P-value <0.0001), while prostate cancers found by screening were more often managed by radical prostatectomy (37.0% vs. 19.1%, P-value <0.0001).

Table 4.1 Demographics

		Screen arm	Control arm	*P-value*
Randomized	**No.**	21,210	21,166	
PC	**No.**	1,339 (6.3%)	298 (1.4%)	*<0.001*
Median age at diagnosis (range)	**Years**	67.0 (53.4-80.7)	69.0 (55.2-80.2)	*<0.001*
PSA at diagnosis (range)	**Ng/mL**	5.5 (0.3-578.0)	11.7 (0.6-2970.0)	*<0.001*
Biopsy Gleason sum	**<7**	840 (67.1%)	97 (42.9%)	*<0.001*
	=7	322 (25.7%)	73 (32.3%)	
	>7	89 (7.1%)	56 (24.8%)	
	missing	88	72	
T stage	**T1C**	569 (42.5%)	94 (31.5%)	*<0.001*
	T2	503 (37.5%)	96 (32.2%)	
	≥T3	228 (17.0%)	80 (26.8%)	
N stage	**N+**	20 (1.5%)	12 (4.0%)	*0.007*
M stage	**M+**	14 (1.0%)	26 (8.7%)	*<0.001*
Treatment	**RP**	495 (37.0%)	57 (19.1%)	*<0.001*
	RT	608 (45.4%)	131 (44.0%)	
	WW	196 (14.6%)	50 (16.8%)	
	ET	40 (3.0%)	60 (20.1%)	
Follow-up (range)	**months**	60.8 (3.1-217.6)	49.5 (2.4-212.7)	

RP= Radical prostatectomy; RT=Radiotherapy;
WW=Watchful Waiting; ET= Endocrine Treatment

Table 4.2 Radical prostatectomy versus radiotherapy

		RP		RT		*P-value*
		Screen	**Control**	**Screen**	**Control**	
PC	**No.**	495	57	608	131	
Median age at diagnosis	**years**	64.3 (55.0-75.3)	66.6 (55.4-73.5)	69.0 (55.2-78.0)	69.4 (55.9-78.1)	*<0.001*
PSA at diagnosis	**Ng/mL (range)**	5.3 (0.6-55.0)	9.3 (2.5-94.0)	6.2 (0.3-259.8)	11.7 (1.3-68.6)	*<0.001*
Biopsy Gleason sum	**<7**	350 (72.8%)	31 (66.0%)	335 (58.1%)	47 (43.1%)	*<0.001*
	=7	113 (23.5%)	12 (25.5%)	184 (31.9%)	36 (33.0%)	
	>7	18 (3.7%)	4 (7.0%)	58 (9.5%)	26 (23.9%)	
	NA	14	10	31	22	
T stage	**T1C**	224 (45.3%)	22 (38.6%)	215 (35.4%)	44 (33.6%)	*<0.001*
	T2	231 (46.7%)	31 (54.5%)	222 (36.5%)	40 (30.5%)	
	≥T3	31 (6.2%)	3 (5.3%)	168 (27.7%)	41 (32.2%)	
Follow-up	**Years (range)**	5.5 (0.1-10.7)	4.9 (0.2-9.9)	4.9 (0.3-10.0)	4.2 (0.2-10.7)	*<0.001*
PSA-progression	**No.**	78 (15.8%)	21 (36.8%)	142 (23.4%)	39 (29.8%)	*<0.001*
Median time from diagnosis to progression	**Years (range)**	2.3 (0.5-8.8)	1.7 (0.4-4.1)	2.2 (0.6-7.4)	2.3 (0.7-5.8)	*n.s.*

RP=Radical Prostatectomy; RT=Radiotherapy; NA=not available

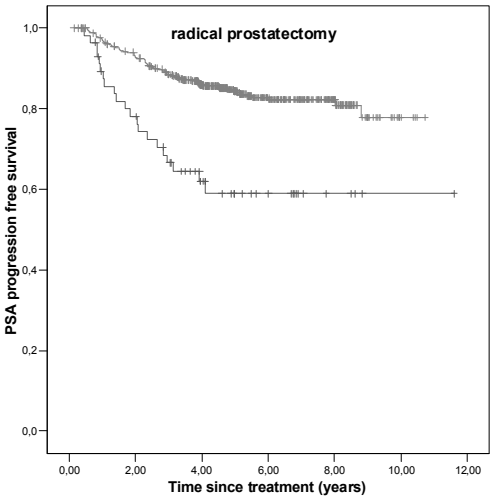

Figure 4.1 Kaplan-Meier projection of the biochemical (PSA-) progression free survival after *radical prostatectomy* in the screen group (top line) and in the control group (bottom line) as a curve of the time period since diagnosis in years.

Men at risk

	0	2	4	6	8	10
screen	495	444	333	162	63	5
control	57	42	23	12	4	1

P-value < 0.001

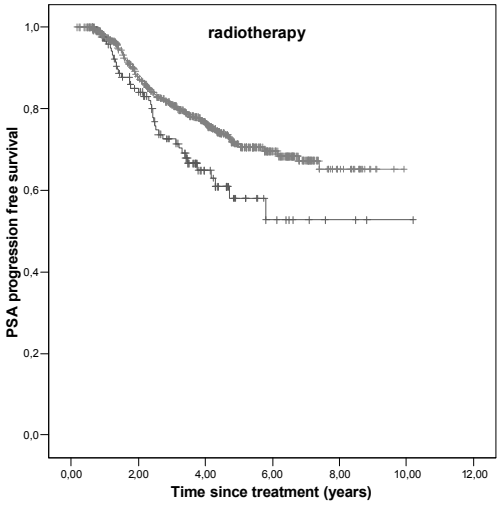

Figure 4.2 Kaplan-Meier projection of the biochemical (PSA-) progression free survival after *radiotherapy* in the screen group (top line) and in the control group (bottom line) as a curve of the time period since diagnosis in years.

Men at risk

	0	2	4	6	8	10
screen	608	501	371	228	82	3
control	131	121	84	57	25	2

P-value 0.01

PSA recurrence rates after radical prostatectomy were significantly lower in the screen arm than in the control arm (15.8% vs. 36.8%, P-value <0.0001; table 4.2). Also after radiotherapy less biochemical progression occurred in screened men than in controls (23.4% vs. 29.8%, P-value 0.01).

As the Kaplan–Meier graphs in figures 4.1–4.3 show, the 5-year PSA-progression free survival rates for radical prostatectomy (84.4% vs. 58.9%; P-value <0.0001), radiotherapy (71.0% vs. 58.0%; P-value 0.01) and endocrine treatment (40.5% vs. 16.3%; P-value 0.04) were significantly higher in screened men than in controls. The median time from diagnosis to progression after radical prostatectomy was 2.3 years (mean 2.5; range 0.5–8.8) in screened men and 1.7 years (mean 1.9; range 0.4–4.1) in controls (P-value 0.4). After radiotherapy the median time to progression was 2.2 years (mean 2.5; range 0.6–7.4) in screened men and 2.3 years (mean 2.3; range 0.7–5.8) in controls (P-value 0.31). After endocrine therapy these times were 1.4 years (mean 1.6; range 0.4–4.1) in screened men and 1.2 years (mean 1.6; range 0.4–4.8) in controls (P-value 0.45).

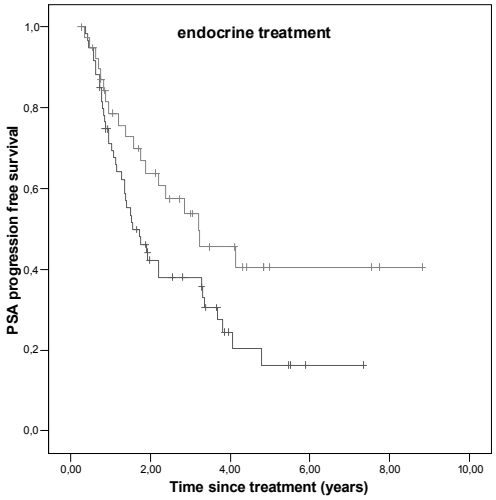

Figure 4.3 Kaplan-Meier projection of the biochemical (PSA-) progression free survival after *endocrine treatment* in the screen group (top line) and in the control group (bottom line) as a curve of the time period since diagnosis in years.

Men at risk

	0	2	4	6	8
screen	40	21	10	3	1
control	60	20	6	1	0

P-value 0.04

DISCUSSION

Although the expected result of screening for prostate cancer, with its shift toward more favorable stages, is a better survival, there are at least two confounders; namely lead-time and length-time bias.[37,44,48,85] Because screening detects cancers before symptoms would have developed, the time period from early diagnosis by screening to death due to prostate cancer is longer than for clinically diagnosed cancers, falsely suggesting a better survival in the screened population (i.e., lead time bias). Calculating the time from randomization to progression could correct for lead-time and this method can be regarded appropriate for the endpoints metastatic disease and prostate cancer-mortality. PSA-progression may be a surrogate endpoint and it is not known whether this method can be used for this purpose.

In the screen arm of this study, 4.8 times more men were diagnosed with prostate cancer than in the control arm. While screening will in the beginning result in the diagnosis of more cancers, an increasing proportion of those cancers will be diagnosed later during the study period (i.e., at a higher age) in the control arm. Although the difference in the number of men diagnosed will become smaller once the follow-up period becomes longer, the difference in the incidence of prostate cancer suggests overdiagnosis, which may be acceptable if it is balanced by a decreasing mortality. This however is not known at present. A mathematical

model based on data from the ERSPC has shown that the mean lead time for prostate cancer is estimated to be 6–12 years, depending on patients' age.[37] This same model estimated that for an annual screening program for 55- to 67-year-olds, 50% of diagnosed cases would constitute instances of overdiagnosis. As a result of length-time bias, the higher incidence of screen-detected prostate cancers can be partly explained by the number of men who are diagnosed with indolent prostate cancer. Those are likely to be more frequent in the screen arm, which dilutes the total group of diagnosed cancers. Because those cancers do not progress, the survival rates in this group are higher as well.

Krygiel et al. found that of 1,939 screen-detected patients 17% had evidence of cancer progression.[86] The percentage with progression-free survival at 5 years for radical prostatectomy was 84%, and for radiotherapy 80%. In our screened population, the progression-free survival after 5 years for radical prostatectomy was 84.4% and for radiotherapy was 71.0%, using the same definitions for biochemical progression. In our study, biochemical recurrence occurred at a median of 2.6 years (mean 2.9; range 0.7–9.1) after surgery of men diagnosed in the screen arm. In the control arm the median time period from surgery to biochemical recurrence was 1.4 years (mean 1.9; range 0.5–4.6). These time periods from treatment to progression corroborate with the recent findings of Freedland et al., who described an American cohort of prostate cancer patients and found a median time from surgery to biochemical recurrence of 2.0 years (mean 3.5).[87] They also reported that the time period between surgery and biochemical recurrence (<3 vs. >3 years) was an independent prognostic factor for prostate cancer specific-survival.

Khuntia et al. reported about 1,352 men diagnosed with T1-T3 prostate cancers after 1987 who were all treated with external beam radiotherapy. Of those men, 63% had no sign of biochemical relapse after 5 years. Our 5-year PSA-progression free survival was 71.0% among screened men and 58.0% among controls.

Albertsen et al. reported that in a cohort of initially untreated men with localized prostate cancer, its mortality persisted to increase even 20 years after diagnosis. Therefore, our follow-up period might be too short, especially considering that Albertsen et al. and others mainly described the natural history of cancers diagnosed before the PSA era. Our study, however, describes a group of cancers found by screening and a control group of men diagnosed during the PSA era. As a result of screening, men diagnosed with prostate cancer are younger and the created lead time will probably result in an even longer time from diagnosis to progression, although this effect was not significant in our study.

Although the use of PSA-progression as an intermediate endpoint is debatable, Pound et al. reported that not a single man who had undergone a radical prostatectomy developed metastases or died of prostate cancer with an undetectable PSA.[88] Freedland et al. reported on 379 men who elected radical prostatectomy and subsequently developed biochemical progression.[87] The 15-year prostate cancer-specific survival since biochemical progression was 55%. The study population of Freedland et al. is collected over a time-span of 18 years,

including some before the PSA era. Nowadays, screening is widely accepted in the US and the population which was studied is a mixture of screened men and those who were not. It is not known to what extent those data are comparable to either the screen arm or the control arm of our study. In general, the PSA-progression free survival can not give a definite indication of the proportion of men dying of prostate cancer, but serves mainly as a tool of comparison.

PSA-testing of asymptomatic men in the control arm of the trial for whatever reason (i.e., contamination) must be closely monitored, because the rate of contamination in the control arm may adversely affect the power of the trial.[76] Otto et al. described that opportunistic PSA testing in the control arm reached a peak within the first months of randomization, after which it decreased.[89] In the control arm of the Rotterdam section of the ERSPC, PSA testing was high, but was not followed by a substantial increase in prostate biopsies. Thus, effective PSA contamination in the Rotterdam section of the ERSPC is low and not likely to jeopardize the power of the trial.[89]

CONCLUSIONS

PSA-screening increases the incidence of prostate cancer and causes a shift toward cancers with more favorable prognostic factors. To what extend the higher PSA progression free survival rates in this study are a result of that shift, and the influence of lead and length-time on these rates is not known. If, and to what extend screening lowers the prostate cancer specific-mortality, and whether this will be in proportion to the burden of screening can not be answered at this moment. Therefore, the definitive results of the ERSPC, which are not expected before 2008, are essential to judge whether population-based screening for prostate cancer is a feasible undertaking.

Chapter 5

Overall survival in the intervention arm of a randomized controlled screening trial for prostate cancer compared to that in a non-screened cohort

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ABSTRACT

Objectives

This population-based study provides comparisons of prostate cancer characteristics at diagnosis of two cohorts of men from two well-defined geographical areas exposed to different intensities of prostate cancer screening. Overall survival in both cohorts was compared to that in the general population.

Patients & Methods

A cohort of 822 men randomized to the intervention arm of a prostate cancer screening trial, and subsequently diagnosed with prostate cancer, was compared to a non-randomized cohort of 947 men whom were clinically diagnosed with prostate cancer in a geographically neighboring region. In both cohorts, cases were diagnosed with prostate cancer between January 1989 and December 1997. A partitioning of overall survival by variables associated with cancer onset such as age-at-diagnosis, stage-at-diagnosis, and grade-at-diagnosis was performed.

Results

Age-at-diagnosis, tumor extent-at-diagnosis, and grade-at-diagnosis were significantly different between the screened and clinically diagnosed cohort. Five-and-ten year survival was higher in the screened cohort than in the clinically diagnosed cohort (88.8% versus 52.4%, and 68.4% versus 29.6%, respectively). Significant differences in survival were evident for all age-, stage-, and grade subgroups, except for metastatic disease-at-diagnosis.

Conclusions

Differences in overall survival favoring the screened population were observed for all baseline characteristics (age-, stage-, and grade-of-disease), and these variables may all explain differences in overall survival as screening achieves early diagnosis as well as a stage-and grade shift. As observed survival rates in the screened population mirrored those within the general population, the contribution of lead time and overdiagnosis to final patient outcome is considered to be large as well.

INTRODUCTION

In previous decades, 50-85% of men with advanced prostate cancer were to die from their disease depending on the age and extent of disease at diagnosis.[90,91] From the early 1990s onwards, the prostate cancer mortality rates have slowly declined in the United States, and in some European countries.[33,92-95] Some have argued that this decrease is due to the application of the serum prostate-specific antigen (PSA) test as a tool for the early detection of prostate cancer.[96,97] Indeed, PSA-determination in serum has contributed to a rapid increase in the incidence of prostate cancer, and a concurrent stage and grade migration to earlier stages and lower grades of disease. However, this effect of screening on grade and stage does not necessarily translate into a reduction of disease-specific mortality as has been shown for lung cancer.[98] Until present, no beneficial effect of prostate cancer screening on mortality using the serum-PSA test, and its subsequent diagnostic and therapeutic sequelae, has been established in properly performed randomized controlled trials.

This study was performed to compare the distribution of prognostic factors at diagnosis in two cohorts of men subjected to different intensities of prostate cancer screening. Furthermore, overall survival in both cohorts was compared to that in the general population. Through this methodology of the expected survival, the magnitude of lead time and overdiagnosis of disease can be estimated. Baseline characteristics of 822 men diagnosed with prostate cancer in the intervention arm of the Dutch section of the European Randomized study of Screening for Prostate Cancer (ERSPC) were compared to those in 947 men clinically diagnosed with prostate cancer in a neighboring geographical region in which prostate cancer screening was not common practice. Cases were diagnosed with prostate cancer during periods of time of similar duration. A partitioning of overall survival by variables associated with cancer onset such as age-at-diagnosis, stage-at-diagnosis, and grade-at-diagnosis was performed in both cohorts.[99,100]

PATIENTS & METHODS

Intervention arm of ERSPC

The ERSPC was designed to study the effect of population-based screening for prostate cancer on prostate cancer mortality and quality-of-life. Between December 1993 and May 1997, in Rotterdam alone, a total of 20,643 men aged 55-75 years were identified in the population registry, invited to participate, and after providing informed consent, randomized to the screening study. A total of 10,456 men were randomized to the intervention arm. Men with a prior diagnosis of prostate cancer were excluded. All participants allocated to the screening arm underwent a serum PSA-test, digital rectal examination (DRE) and transrectal ultrasound (TRUS). A biopsy was advised in those with PSA ≥4.0 ng/mL and/or in those with a finding

suspicious for cancer on DRE and/or TRUS at low PSA-values (0.0–3.9 ng/mL). A systematic lateralized sextant needle biopsy was performed, and one or two additional biopsy cores were taken from hypo-echoic lesions when present. Treatment decisions were at the discretion of the treating urologists thereby considering biopsy tumor features, patient preferences, and life expectancy. A detailed description of the methodology of the screening trial is reviewed by Roobol et al.[101]

Four years after prevalence screen, men were invited to undergo repeated screening (second screening round). At repeat screening, only PSA ≥3.0 ng/mL prompted a biopsy, irrespective of DRE/TRUS-findings.[102] Cancers diagnosed in between the two screening intervals due to opportunistic screening, transurethral resection of the prostate for benign disease, and cystoprostatectomy (i.e., 'interval cancers') were considered as well.[103]

Clinically diagnosed cohort

The clinically diagnosed cohort consisted of men diagnosed with prostate cancer in a well-defined, neighboring geographical area, in the province of 'Zeeland', which is covered by the Rotterdam Cancer Registry. A linkage of incidence and mortality between the municipal civil registries of 'Zeeland' and the Rotterdam Cancer Registry is performed on a regular basis. Men within the cohort were consecutively diagnosed with prostate cancer between January 1, 1989 and December 31, 1997. Access to health care services is similar to that in the Rotterdam area, whereas PSA-determination was not commonly performed as a screening test.

Baseline characteristics

In cases with prostate cancer diagnosed within the intervention arm of the screening trial (n=822), and in those within the clinically diagnosed cohort (n=947), age-at-diagnosis (<55-65 years, 66-70 years, 71-75 years, and ≥76 years), date-of-diagnosis, and histological differentiation grade according to the World Health Organization (WHO) classification (well-, moderately-, poorly differentiated) were obtained.[104] Cases within both cohorts were categorized according to tumor extent: I. Localized disease (cT1 or cT2), II. Regional disease (cT3 or cT4, N1), and III. Distant disease (M1).

Initial treatment modalities (i.e., radical prostatectomy, radiation therapy, androgen deprivation therapy, watchful waiting) were derived from the database of ERSPC, and the Rotterdam Cancer Registry, respectively (table 5.1).

Overall survival

In both cohorts, the time of death irrespective of cause was obtained through a linkage to the municipal civil registries. In the clinically diagnosed cohort, active follow-up of all patients was performed through linkage with the 16 municipal population registries in the province of Zeeland. Each municipal registry provided the Rotterdam Cancer Registry a database with deaths for a given period. Dates of end of follow-up varied from May 23, 2001 to December 1,

2002. In case a patient did not die before the end of follow-up, survival time was calculated from the date of diagnosis to the end of follow-up for his municipal registry. No data on the cause of death was available, as these are susceptible to privacy regulations. Moreover, as the validity and comparability of the cause of death in screening cohorts is questionable using death certificates, overall survival was taken as the final outcome measure.[105]

For all cases within the two study cohorts, duration of survival was defined as the date of prostate cancer diagnosis to the date of death, or to the time of last follow-up if the patient was still alive. It is evident that the survival in the screen-detected cases is positively biased by lead-time.

Statistical analysis

The Chi-square (χ^2) and the Mann-Whitney U test were used to assess the relationship between categorical and continuous variables, respectively, within the intervention arm of the screening trial and the clinically diagnosed cohort. P<.05 was considered statistically significant. Observed and expected survival rates were estimated with Stata freeware subroutine 'strs', which is related to the 'surv2' program. These survival rates were then used to draw survival curves for both cohorts, for men aged 55-75 at diagnosis in both cohorts, and for men aged 55-75 at diagnosis in both cohorts with and without metastatic disease. The expected survival rate is the survival rate in a group of people in the general population, who are similar to the patients with respect to all of the possible factors affecting survival at the beginning of the period, except for the disease under study.[106]

RESULTS

Baseline characteristics

The characteristics of the 822 men diagnosed with prostate cancer in the intervention arm of the screening trial are presented in table 5.1. The median age-at-diagnosis was 67 years (range, 55-78). A description of the 947 men in the clinically diagnosed cohort is given in table 5.1. The median age-at-diagnosis was 75 years (range, 47-95).

Overall survival

The median observation period for patients in the intervention arm was 8.1 years (range, 0.2-11.6), and this was 4.8 years (range, 0.1-13.4) for men in the non-screened cohort. During follow-up, 182 men (22.1% of total) in the screening trial died, whereas this figure was 542 (57.2% of total) for those diagnosed with prostate cancer in the clinically diagnosed cohort. The median age-at-death was 74 years (range, 59-85), and 81 years (range, 51-95), respectively (P<.001). The five-and-ten year survival was higher in the screened cohort than in the non-screened cohort (88.8% versus 52.4%, and 68.4% versus 29.6%, respectively; P<.001) (table

Table 5.1 Baseline characteristics at diagnosis, and primary treatment modalities. A comparison between men diagnosed with prostate cancer within the intervention arm of a randomized controlled screening trial for prostate cancer (randomization between December 1993 and May 1997), and those clinically diagnosed with prostate cancer within a non-randomized cohort (prostate cancer diagnosis between January 1989 and December 1997).

	Clinically diagnosed cohort N (% of Total)	**Screen-detected cohort N (% of Total)**	***P-value** **
Age (years) Median (range)	75 (47-95)	67 (55-78)	*<.001*
<55- 65	151 (16.0)	305 (37.0)	
66- 70	166 (17.5)	260 (31.6)	*<.001*
71- 75	193 (20.4)	244 (29.7)	
≥76	437 (46.1)	13 (1.6)	
Disease extent			
Localized (cT1-cT2)	549 (62.2)	618 (83.1)	
Regional (cT3-cT4, N1)	131 (14.9)	120 (16.1)	*<.001*
Metastasized (M1)	202 (22.9)	6 (0.8)	
Not known or not performed	65	78	
Histological differentiation grade **			
Well	293 (32.8)	551 (67.2)	
Moderately	350 (39.2)	216 (26.3)	*<.001*
Poorly	249 (27.9)	53 (6.5)	
Undetermined/unknown	55	2	
Initial treatment			
Radical prostatectomy	105 (11.1)	298 (36.3)	
Radiotherapy	211 (22.3)	384 (46.7)	
Watchful waiting	89 (9.4)	124 (15.1)	*<.001*
Androgen deprivation therapy ***	439 (46.4)	16 (1.9)	
Other or no treatment ****	103 (10.9)	0 (0.0)	
Total	947	822	

* *The Chi-square (χ^2) test was used for categorical variables and the Mann-Whitney U test was used for continuous variables; undetermined/unknown cases were not included in the analysis*

** *WHO classification system [16]*

*** *Bilateral orchiectomy or LHRH-analogues*

**** *E.g. chemotherapy, transurethral resection of prostate*

5.2). Differences in survival remained for all age-, stage-, and grade subgroups, except for metastatic disease-at-diagnosis.

Overall survival in both cohorts as a function of time after diagnosis, and expected survival rates are depicted in figure 5.1. Figures 5.2-5.4 show the same data for men aged 55-75 years, and for those without and with distant metastasis, respectively.

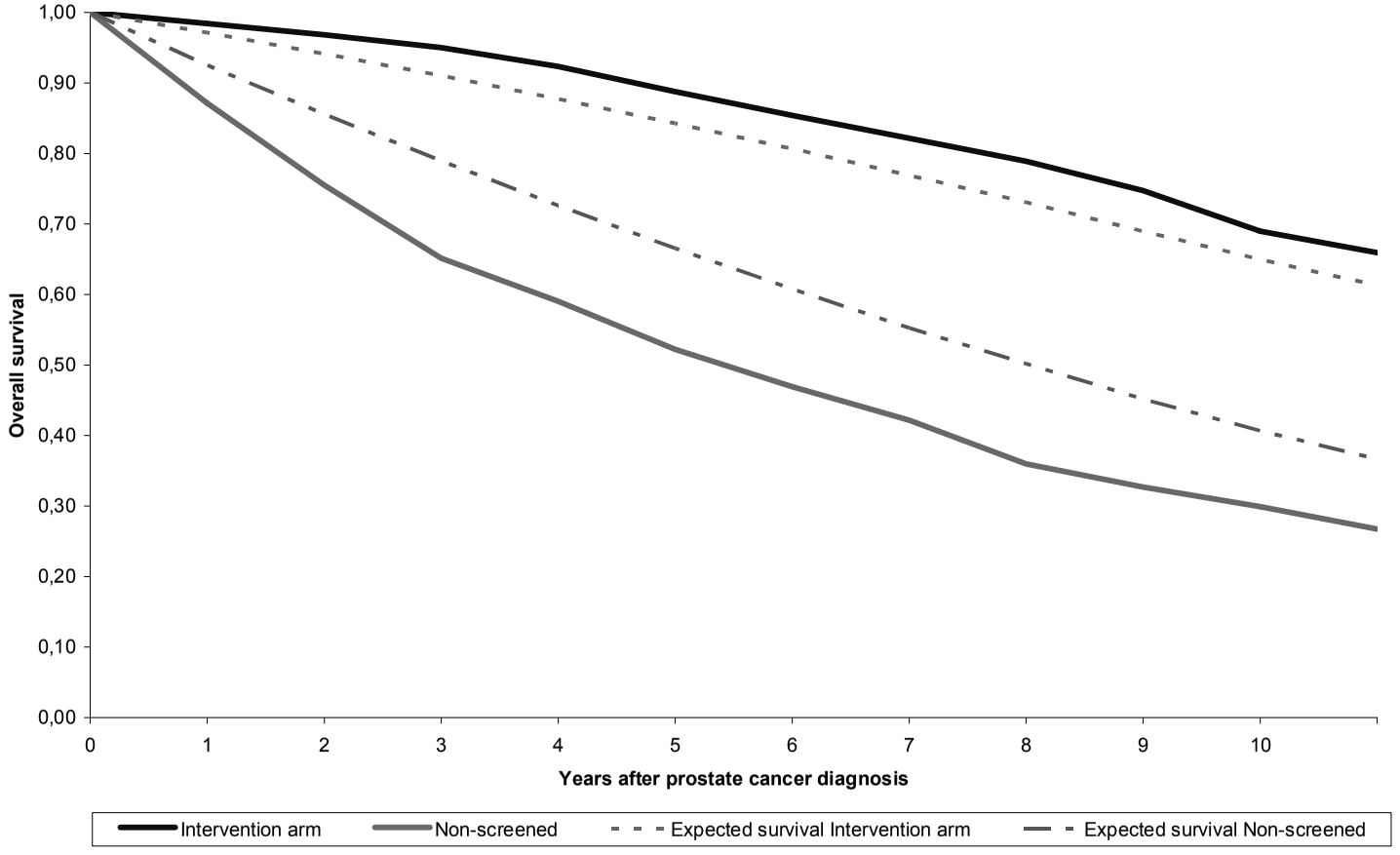

Figure 5.1 Curves showing overall survival for those diagnosed with prostate cancer in the intervention arm of a randomized controlled trial, and those diagnosed with prostate cancer in a cohort not previously subjected to screening as well as the expected survival in men from the general population. Men of all ages, and of all stages.

Table 5.2 Five and ten year survival. A comparison between men diagnosed with prostate cancer within the intervention arm of a randomized controlled screening trial for prostate cancer (randomization between December 1993 and May 1997)(n = 822), and those diagnosed with prostate cancer clinically within a non-randomized cohort (prostate cancer diagnosis between January 1989 and December 1997) (n = 947).

	5-year survival (number of men deceased)		10-year survival (number of men deceased)		*P-value**
Age (Years)	**Clinically diagnosed**	**Screen detected**	**Clinically diagnosed**	**Screen detected**	
<55- 65	72.5 (41)	92.3 (23)	54.7 (50)	80.4 (45)	*<.001*
66- 70	68.7 (52)	90.2 (25)	51.2 (65)	67.8 (57)	*<.001*
71- 75	58.7 (78)	82.8 (41)	29.2 (100)	52.3 (74)	*<.001*
≥76	36.4 (274)	92.3 (1)	12.4 (321)	62.9 (4)	*.003*
Disease extent					
Localized (cT1-cT2)	66.2 (182)	90.2 (59)	38.3 (245)	70.1 (121)	*<.001*
Regional (cT3-cT4, N1)	45.6(70)	81.6 (22)	18.8 (80)	52.1 (42)	*<.001*
Metastasized (M1)	22.3 (156)	33.3 (4)	9.8 (169)	33.3 (4)	*.92*
Histological differentiation grade **					
Well	73.2 (77)	91.4 (46)	45.7 (112)	76.4 (87)	*<.001*
Moderately	52.0 (166)	86.4 (29)	27.6 (210)	62.1 (65)	*<.001*
Poorly	34.4 (163)	73.3 (14)	14.2 (185)	36.4 (27)	*<.001*
Overall	52.4 (445)	88.8 (90)	29.6 (538)	68.4 (180)	*<.001*

* The logrank-test for trend

** WHO classification system

DISCUSSION

The current study provides comparisons of the distribution of prognostic factors and outcomes of two cohorts of prostate cancer patients from two well-defined neighboring geographical areas who were exposed to different intensities of prostate cancer screening. The intervention arm of the ERSPC is known to have a 95% screening coverage, while at the end of 2004, approximately 30% of men in the control arm had their PSA-level measured at least once.[107] This control arm reflects the intensity of screening in the general population, although men enrolled in a screening trial are expected to be more prone to have their PSA tested. The overall survival in a cohort offered systematic PSA-based screening for prostate cancer, and that was subsequently diagnosed with prostate cancer, was longer than the overall survival in a cohort not previously subjected to systematic screening. Five and ten years after diagnosis, the cumulative overall survival differed by 36.4% and 38.8%, respectively (figure 5.1). As the contemporary analysis is non-randomized, the outcomes are likely to be influenced by several other factors than screening itself: (1) differences in overdiagnosis, (2) differences in age-at-diagnosis, (3) differences in stage-and-grade at diagnosis, (4) the intensity and efficacy of treatment modalities, (5) screening biases.

Overdiagnosis

It is well known that screening efforts lead to the detection and treatment of cancers that have no impact on health or longevity, even in the absence of treatment.[37,108] This detection of cancers that would not have surfaced clinically in the absence of screening is called overdiagnosis. The degree of overdiagnosis through screening can in part be estimated by changes in the incidence and mortality rates within the population. For instance, between 1989 and 2003, the age-standardized incidence rates of prostate cancer increased by 48.4% in the Netherlands (reaching 93 cases per 100,000), and by 13.6% in the United States (reaching 165 cases per 100,000).[32,73] The age-standardized mortality rates remained relatively constant in this time period. Accordingly, the incidence-to-mortality ratio in the United States increased from 115 to 34 per 100,000 (ratio, 3.4:1) in 1985 to 174 to 30 per 100.000 (ratio, 5.8:1) in 2006.[33]

In a computer model, Draisma et al. calculated that the rate of overdiagnosis equaled 48% (range, 44-55%) in men aged 55-67 years screened systematically with a 4-year interval.[37] In the intervention arm of the ERSPC, only one in every 30.3 men diagnosed with prostate cancer is likely to succumb of his disease during follow-up, and for every 6.4 deaths, one is due to prostate cancer (data not shown). In screening settings, therefore, the vast majority of men diagnosed with prostate cancer is not likely to die from its disease. Our data further indicate that overdiagnosis was considerable as the observed survival rates in the screened cohort mirror expected survival rates in the general population for all age-, stage- and grade subgroups (figures 5.1-5.3).

Age at diagnosis

In absence of screening, prostate cancer is mainly diagnosed at an older age. In the clinically diagnosed cohort, the median age-at-diagnosis was 75 years, with 33.5% of men having a prostate cancer diagnosis at or before the age of 70 years, and 26.9% after the age of 80 years. In a cohort of 223 patients managed conservatively, prostate cancer mortality was higher among those whose cancer was diagnosed at 70 years or younger than among those whose cancer was diagnosed at older ages.[109] Older men have a higher rate of intercurrent illnesses and death. The proportion of men dying from prostate cancer at any given interval, and for any grade and stage of disease, is expected to be higher in the younger age group.[110] Considering men aged 55-75 years only, overall survival for the cohort as a whole, and for those with non-metastatic disease was significantly higher in those subjected to screening than in those who were not (figure 2-3).

Stage and grade at diagnosis

Evidently, disease extent, and tumor grade at the time of diagnosis have a profound impact on outcome of men diagnosed with prostate cancer. Previous studies have indicated that declines in prostate cancer mortality may be attributed to a decrease in distant disease incidence and distant disease mortality.[91,111] Data from the Surveillance, Epidemiology, and End Result (SEER)

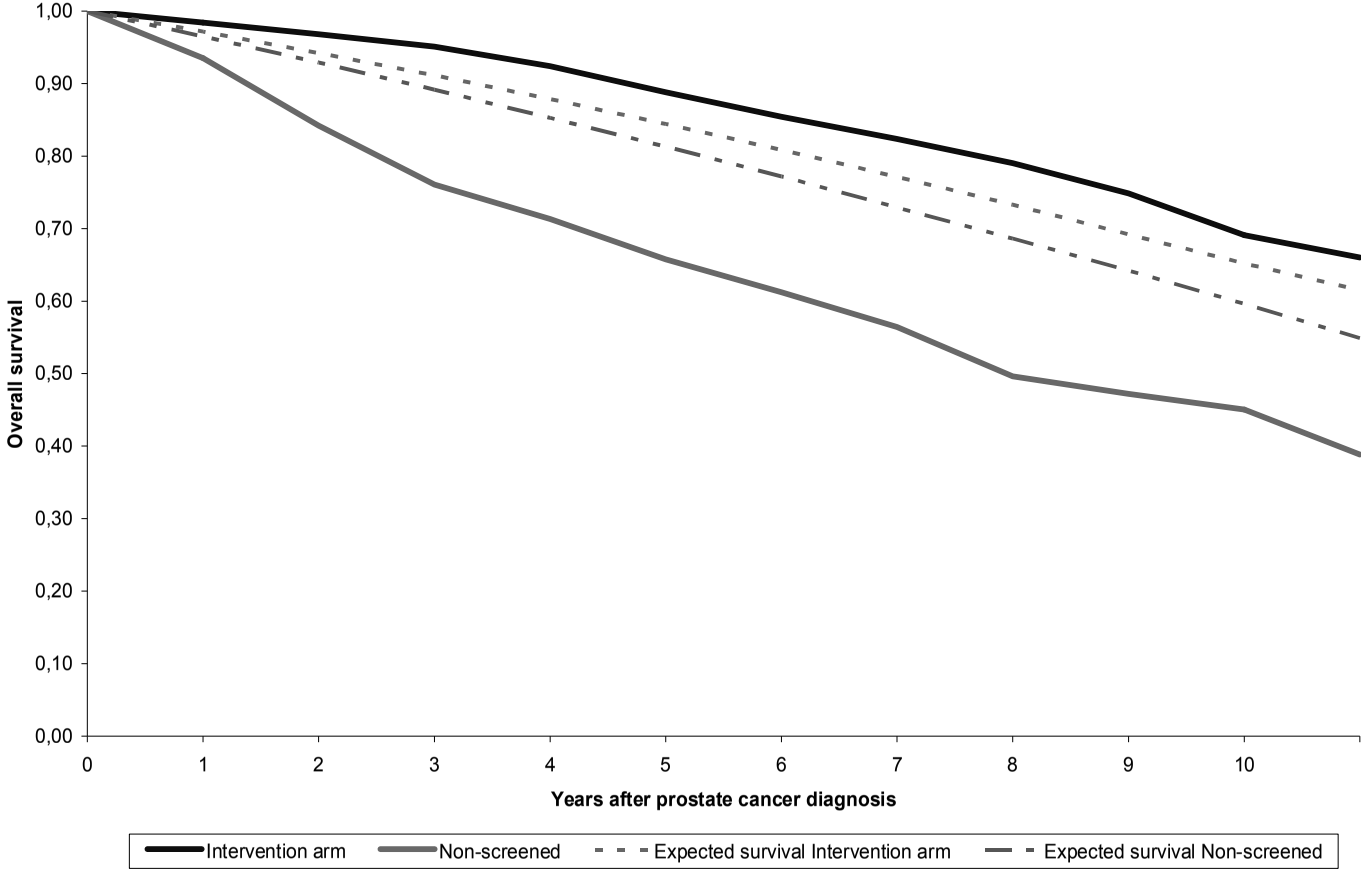

Figure 5.2 Curves showing overall survival for those diagnosed with prostate cancer in the intervention arm of a randomized controlled trial, and those diagnosed with prostate cancer in a cohort not previously subjected to screening as well as the expected survival in men from the general population. Men aged 55-75 years, and of all stages.

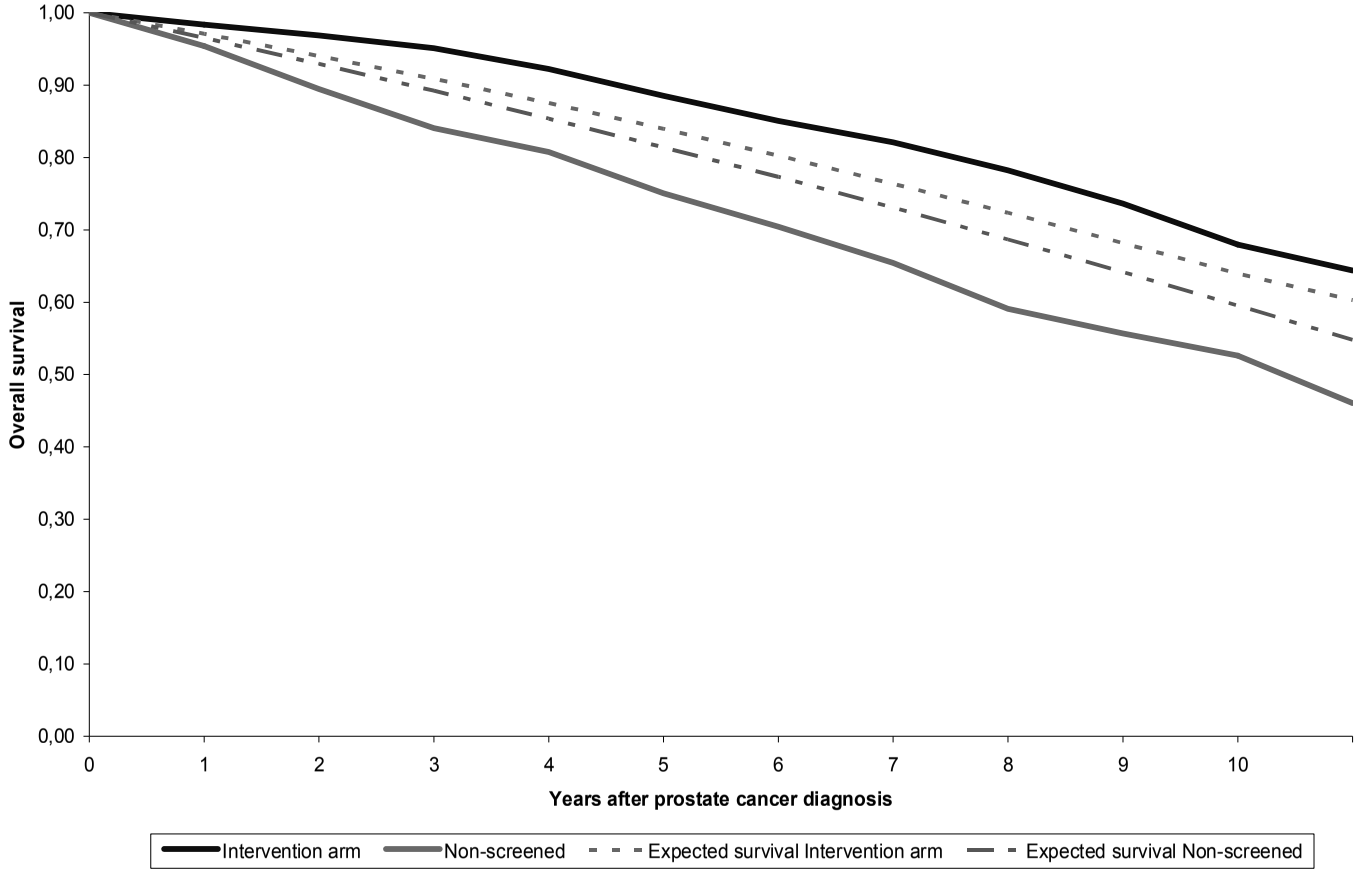

Figure 5.3 Curves showing overall survival for those diagnosed with prostate cancer in the intervention arm of a randomized controlled trial, and those diagnosed with prostate cancer in a cohort not previously subjected to screening as well as the expected survival in men from the general population. Men aged 55-75 years, and with non-metastasized disease (M0).

Program indicate that overall survival rates for patients with distant disease were 80%, 49%, and 33% after 1-, 3-, and 5-years follow-up, respectively.[96] As comparison, men with regional stage disease (cT3-cT4, N1) had 1-, 3-, and 5-year relative survival rates of 100%, 100%, and 98%, respectively. A rapid reduction in prostate cancer deaths may therefore be explained by the detection and subsequent treatment of cancers in their localized or regional stage-of-disease before they have metastasized. The finding that distant stage disease was a relative rare finding in the intervention arm of the screening trial compared to that in the clinically diagnosed cohort (i.e., 0.8% to 22.9% of diagnosed cases, respectively) is likely to explain at least in part the differences in overall survival.

Studies on the natural history of clinically localized prostate cancer in population-based cohorts indicate that men most likely to succumb of prostate cancer as early as 5 to 10 years after diagnosis were those with moderately or poorly differentiated tumors (i.e., Gleason scores 7 and 8-10, respectively; WHO 2 and 3, respectively).[109,110] Those with well-differentiated tumors (i.e., Gleason scores 2-6; WHO 1) rarely died from the disease. Furthermore, SEER data indicate that relative survival rates of those with poorly differentiated prostate cancer were 100%, 96%, and 87% after 1-, 3-, and 5-years of follow-up, i.e., evidently higher than those with distant stage disease. In a survival model, correcting for lead time and overdiagnosis rates by age, Parker et al. predicted that the absolute survival benefit of radical treatment for screen-detected prostate cancer was greatest in those with higher grade disease.[112] Our data indicate that screening efforts provide for a window of curability as a large proportion of screen-detected cases have moderately-and poorly differentiated disease (table 5.1).

Intensity and efficacy of treatment modalities

Improvements and refinements in techniques of radical treatment for localized disease such as radical prostatectomy and external beam radiation therapy may have influenced declining mortality rates.[113,114] Men in the intervention arm of the screening trial were more likely to have curative radical prostatectomy or radiotherapy than their counterparts in the non-screened cohort (table 5.1). This finding might at least partly have driven mortality rates down. Other explanations for the reported declines in mortality rates have been the early application of anti-androgen therapy in advanced disease.[115,116] The application of androgen-deprivation treatment in men in a relatively early phase of disease may have delayed disease progression to metastatic disease or death for several years, or until some of patients die of intercurrent illnesses.

Screening biases

Screening cohorts have increased survival rates compared to non-screened cohorts due to lead time (i.e., the time by which a screening test advances the diagnosis of disease) and length time (i.e., the detection of slowly growing, non-aggressive tumors).[117] The magnitude of both lead and length time in prostate cancer screening trials is largely unknown, though it is estimated that lead time ranges between 3 and 12 years depending on age, tumor stage

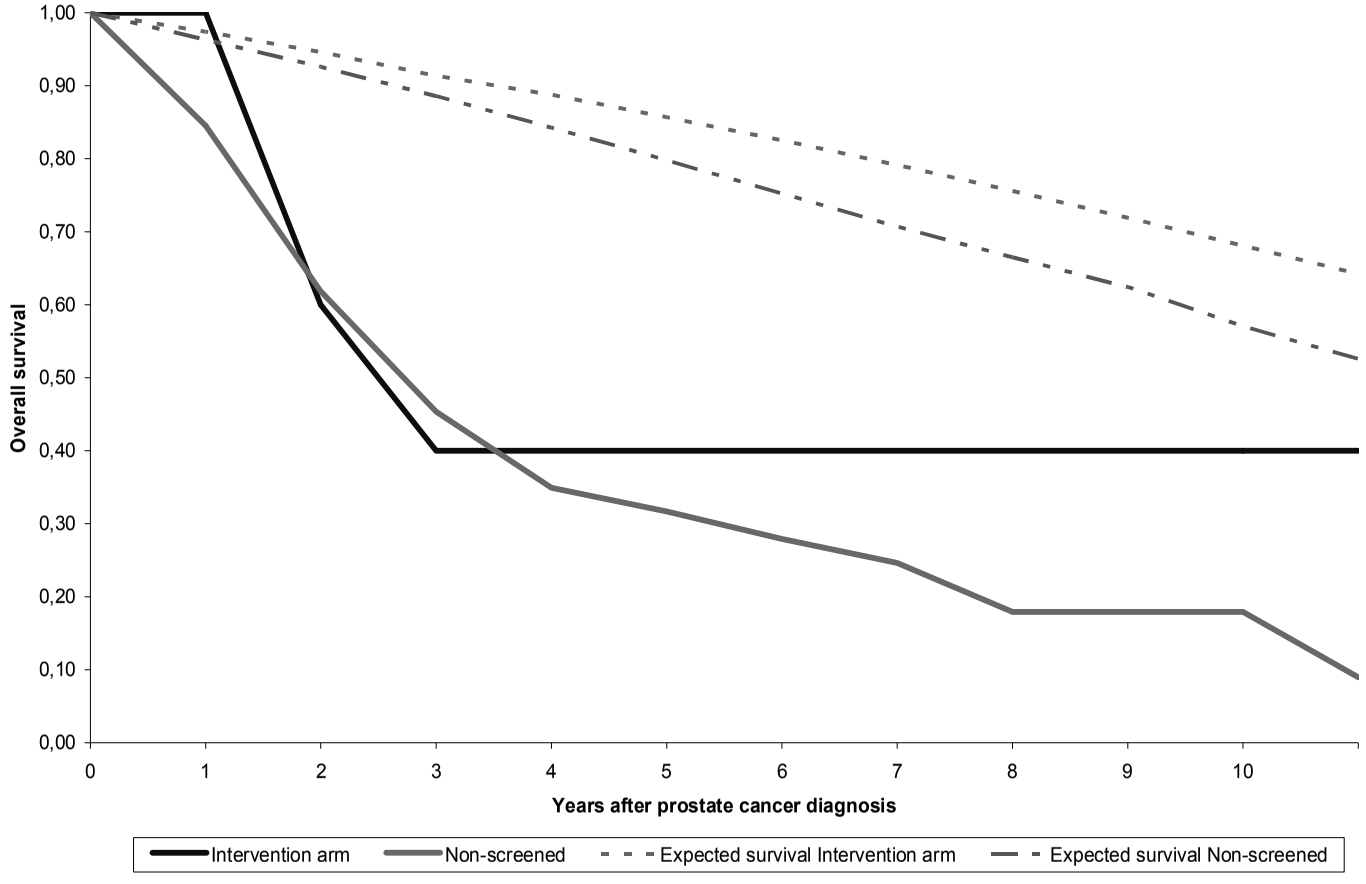

Figure 5.4 Curves showing overall survival for those diagnosed with prostate cancer in the intervention arm of a randomized controlled trial, and those diagnosed with prostate cancer in a cohort not previously subjected to screening as well as the expected survival in men from the general population. Men aged 55-75 years, and with metastasized disease (M1).

and tumor grade.[37,118] The effect of length time is expected to be limited as the number and aggressiveness of interval cancers is relatively low.[103] In fact, with a 4-year screening interval, none of the detected interval cancers were poorly differentiated or metastatic. In many patients in the present cohort, the follow-up period may not have surpassed the survival time after a cancer diagnosis with added lead time. On the other hand, lead time of patients who present clinically with distant disease is probably shorter than those who present with localized or regional disease, and most cases with aggressive disease beyond cure have probably surfaced ('progressed') on follow-up. By definition, these cases are at increased risk of dying from the disease.

Differences in the composition of, and risk factors in the male cohorts (e.g., smoking habits, presence of comorbidities and concomitant diseases) might have influenced endpoints apart from age-, stage-, and grade differences. For instance, men with synchronous malignant tumors (except for basal cell carcinomas) were excluded from randomization in the screening trial, whereas these men were included in the survival analysis in the non-screened cohort. Also, participants of screening trials are probably more health aware, more likely to have a healthy lifestyle, to seek for medical care, and to comply to treatment ('healthy attendee bias').[119] These two observations implicate that men in the intervention arm of the screening trial were healthier than men in the clinically diagnosed cohort, and probably even healthier than men in the general population (see also: figures 5.1-5.3). How and to what magnitude these selection biases affect the outcome of these two cohorts was not possible to assess. Only prospective, properly performed, randomized clinical trials will avoid most of these biases, and will give a final answer to the question whether screening for prostate cancer is beneficial, or not [38].

CONCLUSIONS

The overall survival rate in a contemporary series of men diagnosed with prostate cancer within a population-based screening trial was longer than that of men in a non-randomized cohort clinically diagnosed with prostate cancer in a geographical adjacent region. Differences in survival were observed for all ages, and for all stages and grades-of-disease, except for metastatic disease-at-diagnosis.

Differences in baseline characteristics (age-, stage-, and grade-of-disease) between cohorts may all explain differences in overall survival as screening achieves early diagnosis as well as a stage and grade shift. Furthermore, as observed survival rates in the screened population mirrored expected survival rates in the general population, the contribution of lead time and overdiagnosis of disease to final patient outcome is believed to be considerable. Data reported herein do not yet provide evidence of screening efficacy, as all possible biases may largely account for the observed differences in overall survival.

Chapter 6

Feasibility study of adjustment for contamination and non-compliance in a prostate cancer screening trial

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ABSTRACT

Background

The use of PSA as a screening test has become increasingly prevalent in the general population and therefore also in the control arm of the European Randomized study of Screening for Prostate Cancer (ERSPC). We present a feasibility study and impact simulation of a secondary analysis, which imitates a situation where all participants in the study are managed according to their random assignment.

Methods

The results of the Rotterdam section of the ERSPC were adjusted for contamination and non-compliance according to Cuzick et al. (1997). Endpoints of this analysis were simulated reductions in prostate cancer mortality.

Results

Of the men allocated to the screen arm, 27.1% were non-compliant. In the control arm 30.7% had their PSA-level measured by a general practitioner (i.e. contamination). For a scenario in which the intention-to-screen analysis was assumed to give a decrease in the mortality in the men randomized to screening of 6.7%, the secondary analysis resulted in a decrease of 16.1% for those actually screened.

Conclusion

Although the definition of contamination as 'PSA ever tested' gives an indication of the proportion of contamination, it will be important to differentiate the screening use of PSA from its diagnostic use. For the rest, adjustment for non-compliance and contamination was shown to be feasible in this prostate cancer screening trial. It can therefore be used to carry out a secondary analysis on the definitive outcome of the ERSPC and will provide accurate information for those men who are in fact screened.

INTRODUCTION

Prostate cancer is after lung cancer the most important cause of cancer-related death in American males.[33] With the introduction of PSA in the late 1980s, a screening tool became available, which has proved to detect prostate cancers earlier in the course of the disease.[24] Although the prostate cancer mortality in the US has decreased over the last decade, a differentiation between possible screening effects and other possible causes, such as more effective treatments, has not been possible. Whether screening results in a lower prostate cancer mortality is therefore still unclear.

Four case-control studies evaluating the effect of screening have been published; only two found an effect on the endpoint under study.[34-36,120] The most recent case-control study by Concato et al. did not show an effect of screening. Since case-control studies are inevitably biased, it is important to await the results of the two ongoing randomized controlled trials evaluating prostate cancer screening: (1) the Prostate, Lung, Colon and Ovarian (PLCO) cancer screening study and (2) the European Randomized study of Screening for Prostate Cancer (ERSPC).[18]

Ideally, in a randomized screening trial the use of screening should be limited to men in the screening arm. However, the freedom of choice cannot be denied to participants in either arm. Contamination is defined as the use of screening in the control arm. Another process that dilutes the effects of screening is non-compliance. Non-compliers are participants allocated to the screening arm of a trial, who do not undergo screening or parts of the screening process. Various methods were described to get a more realistic impression of the real effect screening has.[121,122] The method described by Cuzick et al. offers a possibility to evaluate a randomized screening study by adjusting for non-compliance and contamination. Such a secondary analysis imitates a situation in which all participants in the study are managed according to the random assignment and provides an unbiased estimate of the effect of screening in those prepared to accept it, as contrasted to the conventional intention-to-screen analysis which estimates the on a whole population offered screening.[122]

Although no population based prostate cancer screening programs exist in the countries participating in the ERSPC, the use of PSA as a screening tool has become increasingly prevalent, thereby leading to contamination in the control arm. The ERSPC was powered to detect a 25% difference in prostate cancer-specific mortality in the presence of a 20% contamination rate.[78] The model of Cuzick et al. is likely to be helpful for the evaluation of the net effect of screening. It is unclear whether the Rotterdam center is capable of collecting the required data for such a secondary analysis. We therefore present a feasibility study and impact simulation of adjustments for contamination and non-compliance applied to the Rotterdam section of the ERSPC.

PATIENTS & METHODS

The ERSPC is a randomized controlled trial carried out in eight European countries and studies the effect of screening for prostate cancer in terms of prostate cancer specific mortality, quality of life and costs. In the Netherlands alone 42,376 men were randomized to the screening (n=21,210) or the control arm (n=21,166) from June 1993 through December 1999. The conditions and algorithm of the ERSPC are described in greater detail elsewhere.[21]

Screening arm

From December 1993 through May 1997 all men with suspicious findings on digital rectal examination and/or trans-rectal ultrasound and all men with a PSA ≥ 4.0 ng/mL were invited for biopsy. After May 1997, digital rectal examination and trans-rectal ultrasound were omitted as screening tests and the PSA-threshold value for biopsy was lowered to 3.0 ng/mL. All men in the screen group who were still eligible for screening after four years were reinvited for repeated screening. From June 1994 to March 1996 an early re-screen study was conducted to evaluate the value of a 1-year re-screening after a benign biopsy result.

Control arm

The 21,166 men in the control arm of the ERSPC were not invited for PSA testing and in case of symptoms received standard medical care, which meant that general practitioners (GPs) and local urologists provided the evaluation of symptoms and a diagnosis of prostate cancer. Men with prostate cancer in the control arm were identified through a linkage with the Comprehensive Cancer Registry.[79] For this report, the cut-off date for diagnosed prostate cancers was January 1st 2005 in both the screen and the control arm.

Endpoint

The primary endpoint of the ERSPC is prostate cancer-specific mortality. This main endpoint of the study is subject to confidentiality at the level of the independent data monitoring committee, which carries out interim evaluations as indicated in the published evaluation plan.[78] For this report, we have therefore used simulated prostate cancer mortality rates as endpoints, which were varied in order to study the effect of contamination and non-compliance on possible different levels of prostate cancer mortality reduction.

Non-compliance

Non-compliance was defined as non-participation in the screening program after randomization for men allocated to the screening arm. In this study, all men who completed the first round of the screening program and subsequently followed the screening program's protocol were labeled as compliers. Men who died, were diagnosed with an interval carcinoma or reached the age limit of the study protocol of our screening program (i.e. age ≥ 75), were not classified as non-compliers.

Contamination

Contamination was defined as the use of PSA screening in the control arm of the study. PSA screening was defined as the measurement of at least one PSA level by the patient's GP after randomization. Ideally one should only consider tests taken for the purpose of screening, i.e. in non-symptomatic men. The ability to ascertain this will be studied in a future report. Data on PSA tests performed in the period from randomization through January 1st 2005 were obtained from the laboratory of the general practitioners (GP laboratory) in Rotterdam.

Model for adjustment of contamination and non-compliance

Cuzick et al. have described a procedure to adjust randomized controlled trials for contamination and non-compliance.[122] The rationale is described elsewhere but can be summarized as follows: figure 6.1 illustrates that the proportion of non-compliers and associated endpoints in the screen arm are also accounted for in the control arm as 'potential non-compliers'. The remaining participants are called 'compliers' (screening arm) and 'potential compliers' (control arm). Subsequently, the same is done for the contaminators in the control arm. The remaining cases fall in two groups ('ambivalent') in which the real effect of screening can be studied. A Taylor series expansion with a correction for the sampling of controls was used for calculation of the imaginary confidence intervals. The method for adjustment for non-compliance and contamination leads to wider confidence intervals due to a lower number of participants than in the intention-to-screen analysis. This is likely to be compensated by a gain in effect and is therefore expected to have little impact on power, but does affect the results.

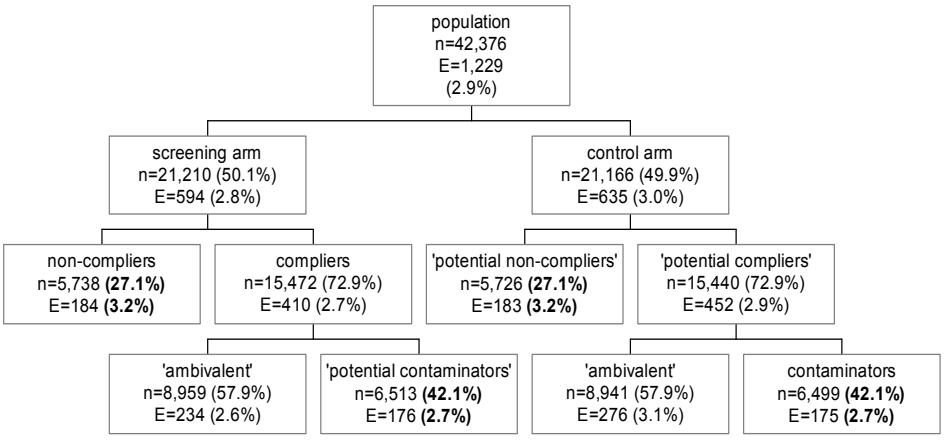

Figure 6.1 Flowchart of the model, which adjusts for non-compliance and contamination; an example

N = number

E = Endpoint

The bold percentages are identical

The lifetime risk of dying from prostate cancer in the US was 2,97% based on years 2000-2002 in the SEER database. For this impact simulation, we assumed that the prostate cancer specific mortality of men in the control arm was 3.0% of the number of men randomized. We calculated the relative risks for three different scenarios: (1) screening for prostate cancer has no effect on the prostate cancer mortality (prostate cancer mortality is 3.0% in both the screen and the control arm), (2) the effect of screening on the mortality is small (prostate cancer mortality in the screen arm 2.8%, a reduction of 7%), and (3) the effect on the mortality is large (prostate cancer mortality in the screen arm 2.0%, a reduction of 33%).

RESULTS

From 1993 to 2005, the screening program in Rotterdam has detected 1,712 prostate cancers; 134 cancers were diagnosed in between two screening rounds (i.e. interval cancers). During the same period, 521 cancers were diagnosed in men allocated to the control arm.

Non-compliance

Different types of non-compliance exist: some men refused to have their PSA drawn and some refused a biopsy indicated by screening. The latter can be a result of a medical contra-indication as well. Both events of non-compliance occurred in multiple variations during the different screening rounds.

Table 6.1 shows that in round one 1,240 men (5.8%) refused a PSA test, in the early re-screen round 332 (20.7%), in the second round 2,856 (15.4%), and in the partial third round (until January 1st 2005) 655 (5.5%), which adds up to 5,083 men (24.0%) who did not fully

Table 6.1 Non-compliance in the screening arm of the Rotterdam section of the ERSPC

		Round 1	Early re-screen	Round 2	Round 3*	Total
Eligible for screening		21,210	1604	18,504	11,982	
No PSA-test	***Interval carcinoma***		7	109	18	**134**
	Dead		25	716	222	**963**
	Too old		24	2,348	929	**3,301**
	Other	1,240	332	2,856	655	**5,083**
Biopsy indication	***Done, no PC****	4,117	509	2,913	447	**7,986**
	Done, PC	1,014	68	550	80	**1,712**
	No, medication*	88	11	55	6	**160*** **
	Refuses after PSA*	327	30	175	21	**553*** **
No biopsy indication*		14,424	668	9,389	2,074	**26,555**

* *Incomplete; cut-off date 01-01-2005*

** *To next screen round*

*** *In total 655 men did not have a biopsy at least once, while a biopsy indication was present.*

comply with the screening program considering only the PSA determinations. 655 men (3.1%) did not fully comply with the screening program. They underwent the PSA test, had a biopsy indication but were not biopsied. The sum of these two (5,083 + 655 = 5,738; 27.1%) was the number of non-compliers used in the model.

Contaminators

The regional GP laboratory covers besides the municipality of Rotterdam 7 of the 12 neighboring municipalities, or 16,455 (77.7%) out of 21,166 control men, from which the trial participants were recruited. The group of GPs who are participating in the Rotterdam GP lab were not likely to be biased for demanding PSA tests. We therefore extrapolated the proportions to the control arm as a whole. The ability to ascertain this will be studied in a future report. The GP-laboratory covered 16,455 (77.7%) out of 21,166 men allocated to the control arm of the ERSPC. In those, 11,417 PSA-tests were performed in 5,004 men (30.4%) (mean 2.3 tests/man; range 1-22). Table 6.2 shows the PSA values of all tests performed, per participant and per detected prostate cancer, together with the calculated positive predictive value (PPV). Considering the coverage of the GP laboratory after extrapolation 6.499 men (5,004 / 77.7%) were used as contaminators in the analysis, which is 30.7% of 21.166.

Table 6.2 PSA recordings in the control group population retrieved from the GP laboratory

PSA (ng/mL)	*Tests (%)*	*Men* (%)*	*Prostate cancers** (%)*	*PPV****
All values	*11,417*	*5,004 (30.4%)*	*243 (1.5%)*	*4.9%*
0-1.0	3,250 (28.5%)	1,566 (31.3%)	1 (0.4%)	*0.1%*
1.0-2.0	3,080 (27.0%)	1,428 (28.5%)	8 (3.3%)	0.6%
2.0-3.0	1,552 (13.6%)	667 (13.3%)	8 (3.3%)	1.2%
3.0-4.0	1,019 (8.9%)	386 (7.7%)	8 (3.3%)	2.1%
4.0-5.0	710 (6.2%)	252 (5.0%)	17 (7.0%)	6.7%
5.0-6.0	487 (4.3%)	148 (3.0%)	19 (7.8%)	12.8%
6.0-7.0	343 (3.0%)	132 (2.6%)	16 (6.6%)	12.1%
7.0-8.0	242 (2.1%)	107 (2.1%)	22 (9.1%)	20.6%
8.0-9.0	142 (1.2%)	43 (0.9%)	19 (7.8%)	44.2%
9.0-10.0	124 (1.1%)	45 (0.9%)	18 (7.4%)	40.0%
10.0-20.0	331 (2.9%)	134 (2.7%)	51 (21.0%)	38.1%
>=20.0	137 (1.2%)	96 (1.9%)	56 (23.0%)	58.3%
Mean; median (range)	*3.8; 1.7 (0.1-1,764.8)*	*4.6; 1.5 (0.1-1,764.8)*	*38.0; 9.1 (0.8-1764.8)*	

The data account for 77.7% (16,455 / 21,166) of men who lived in the region of the GP-laboratory.

* *In case more PSA tests were performed in one patient, the first test is used for calculations.*

** *In case more PSA tests were performed in one patient, the last test is used for calculations.*

*** *PPV=Positive predictive value; the number of diagnosed cancers divided by the number of men tested for PSA.*

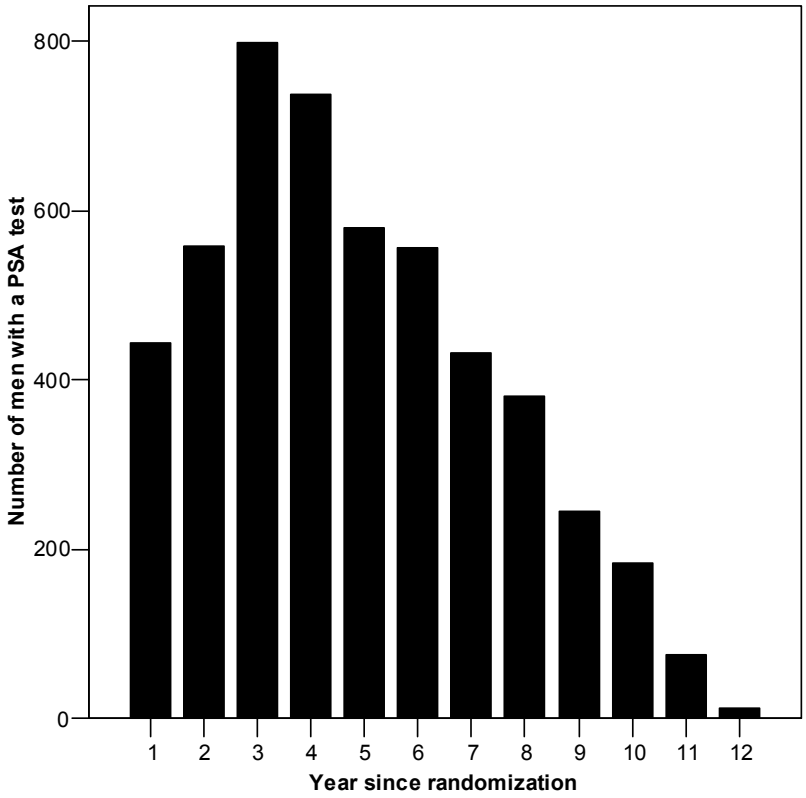

Figure 6.2 Timing of the first PSA-test after randomization of men in the control group of the Rotterdam section of the ERSPC

Before 2005, 521 cancers were diagnosed in men allocated to the control arm of the ERSPC. Of those, 243 (46.6%) men had had their PSA tested by their GP; after extrapolation to the whole control group population 316 prostate cancers (60.7%) were considered to be diagnosed after a PSA recording by their GP. The mean delay between the first PSA recording and prostate cancer diagnosis, either by needle biopsy or TURP, was 19.8 months (median 8.5; range 0.13-87.9). A first PSA-recording within a half-year before prostate cancer diagnosis was present in 113 of the 243 men (46.5%). Figure 2 shows the time period from randomization to PSA test-date.

IMPACT SIMULATION

Three scenarios for the effect of prostate cancer screening were simulated using the contamination and non-compliance rates described above (table 3).

Table 6.3 Assumptions of endpoint proportions (endpoint/number of men) for men in three different scenarios. The results, with use of the proportions in the 'total' column are shown in table 4

	Screen			Control		
Scenario for endpoints	**Non-compliers**	**Compliers**	**Total**	**Contaminators**	**Non-contaminators**	**Total**
1	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%
2*	3.2%	2.7%	2.8%	2.7%	3.1%	3.0%
3	3.0%	1.6%	2.0%	2.0%	3.7%	3.0%

Scenario 1 *No effect of screening*
Scenario 2 *Small effect of screening*
Scenario 3 *Large effect of screening*
** Example used in fig. 1 and in the text*

Table 6.4 Effect differences between the intention-to-screen analysis and the secondary analysis (i.e. after correction for non-compliance and contamination as illustrated in figure 1). The numerator is the number of men who reached the endpoint. The denominator in the proportions is the number of men randomized

Scenario	*Intention-to-screen*		***Difference***	*Secondary analysis*		***Difference***	*Point estimates (95%CI)*	*Absolute gain in effect*
	Screen	**Control**		**Screen**	**Control**			
1	3.0%	3.0%	**0.0%**	3.0%	3.0%	**0.0%**	**0.0 (0.78-1.30)**	0.0%
2	2.8%	3.0%	**0.2%**	2.6%	3.1%	**0.5%**	**0.85 (0.65-1.11)**	0.3%
3	2.0%	3.0%	**1.0%**	1.4%	3.7%	**2.4%**	**0.33 (0.22-0.45)**	1.4%

95% C.I. 95% confidence intervals

The first scenario assumes that screening has no effect. The results of the intent-to-screen and the secondary analysis are comparable, although confidence intervals will be larger after correction. The second scenario assumes that screening has just a minor effect on the prostate cancer mortality.

Table 6.4 and figure 6.1 show that of men allocated to the screening arm 27.1% are non-compliers and of these 3.2% have reached the endpoint. These proportions are used to calculate the number of 'potential non-compliers' (n=5,726) with the associated number of men who reached an endpoint (n=183) in the control arm. The remainder equals the group of 'potential compliers' (n=15,440) with 452 men (635-183) who reached the endpoint. Subsequently, 6,499 men (42.1% of the 'potential compliers') of men allocated to the control arm of the study had a PSA test done (i.e. contaminators), with 175 men (2.7%) who reached the endpoint. These proportions have to be transferred to the screening side of figure 6.1. In this way 6,513 'potential contaminators' are identified with 176 men who reached the endpoint.

The remaining 'compliers' and 'potential compliers' then equal the 'ambivalent' 8.959 men with 234 endpoints reached (2.6%) in the screening arm and 8,941 men with 276 endpoints (3.1%) in the control arm. The intent-to-screen analysis gives a benefit in survival of 0.2%, which amounts to a reduction of 7%; after adjustment however, this effect was 0.5%, which amounts to a reduction of prostate cancer mortality in this constructed example of 16.7%. If screening has a larger effect on prostate cancer morality rates, as simulated in scenario 3, both, the intention-to-screen and the corrected analysis will indicate this significant difference.

DISCUSSION

The method for adjustment used in this paper has been applied to breast cancer screening trials before.[123] This paper describes the first use of a screening related secondary analysis in a prostate cancer screening trial. The only randomized prostate cancer screening trial analyzed so far is the Quebec study.[124,125] The way the data of this study were analyzed contrasts sharply with our methodology and plans. A secondary analysis allows to consider what the outcome is for those men who comply with all aspects of screening, it gives an answer to the question "what happens to me if I get screened". The intention to screen analysis allows to judge what happens if a screening program is applied to the general population.

The Rotterdam centre has access to computerized data of PSA use in the area and the possibility of retrieving prostate cancer incidence data of men in the control arm of the study. Since data on contamination and non-compliance are reliably available for ERSPC Rotterdam, the method used in this report is feasible for this adjustment and can therefore be used in a secondary analysis. Within the Rotterdam section of the ERSPC, 72.9% of men allocated to the screen arm were fully screened in our screening program until January 1st 2005. Meanwhile, 30.7% of men allocated to the control arm of the study had their PSA tested by their GP at least once. If a reduction in prostate cancer mortality by screening from 3.0% to 2.8% was assumed for the intention–to-screen analysis (scenario 2), adjustment for contamination and non-compliance led to a larger decrease of 0.5%. These figures translate into potential mortality reduction in the intention-to-screen and secondary analysis of 6.7% and 16.7%.

Non-compliance

Different moments and levels of non-compliance occurred: men can refuse to have their PSA drawn and it is possible that men subsequently refuse an indicated biopsy. The latter can be a result of a medical contra-indication as well. Both events of non-compliance can occur in multiple variations during the different screening rounds and therefore influence the clear rate of compliers in different ways. Compliers in this study are defined as those men who fully complied with the screening program. A secondary analysis in which men with different types of non-compliance are included as subgroups will be subject of future study.

Contamination

In trials such as the ERSPC, PSA contamination, i.e. testing of asymptomatic men in the control arm of the trial for whatever reason must be closely monitored. The rate of contamination in the control arm may adversely affect the power of the trial. Beemsterboer et al. evaluated opportunistic PSA testing in the first 1.5 years of the ERSPC, Rotterdam section.[126] They reported that after randomization, approximately 8% of the men in the control arm received 1 or more PSA tests each year. Otto et al. have also studied contamination in the Rotterdam section of the ERSPC.[89] In the period evaluated, July 1st 1997 to May 31 2000, 20.2% of men in the control-arm had at least one PSA-test done after randomization. We studied the same cohort, but with a different time frame, namely from randomization to January 1st 2005, during which 30.4% had their PSA tested by their GP. The use of PSA as a screening test has become more common during recent years, which explains the increase in the number of men tested.

Ciatto et al. reported on the PSA contamination in the different centers of the ERSPC.[127] Low contamination rates were reported from the Netherlands (13.9%) and Spain (6.7%), whereas the frequency of opportunistic screening was higher in other centers, especially Italy (36.6%). However, these differences can at least in part be explained by the various methods (database linkage, self-administered questionnaires and interviews) by which the data were obtained.

The definition of contamination we have used in this paper is likely to overestimate the rate of contamination, because some of the PSA tests were done because they were medically indicated. On the other side, some men in the control arm are likely to be diagnosed as a result of screening use of PSA by medical specialists who do not use the GP laboratory. A limitation of our study is that not all PSA tests performed outside the trial could be traced, since the regional GP laboratory does not cover all municipalities in which recruitment was carried out. We have no evidence of PSA testing carried out by physicians in the regional hospitals; however, in the Dutch healthcare system, patients are only referred to a specialist after referral by their GPs, implying that these men were most likely symptomatic and a PSA test ordered would rather be diagnostic than opportunistic testing. Another limitation of this study is that the time period between randomization and contamination was not taken into account. In order to obtain a more precise estimation of the reasons for the use of PSA, a differentiation between screening and diagnostic applications will be made. Furthermore, research into the results of PSA tests in terms of the proportion in which they lead to a prostatic biopsy indicated by a given test is important. The former can be achieved by sending questionnaires to the GPs of patients who had their PSA tested. The latter can be obtained by a link with the national pathology registration, which covers all reports of pathologists working in the Netherlands.

CONCLUSIONS

Adjustment for non-compliance and contamination is an important undertaking when an intervention such as PSA testing is also used in the control arm of a randomized screening trial. Since data on contamination and non-compliance are reliably available for ERSPC Rotterdam, the method used in this report is feasible for this adjustment and can therefore be used in a secondary analysis. This will be of importance especially if screening has just a minor effect on mortality from prostate cancer with the intention-to-screen analysis. Although the definition of 'ever having had a PSA test' gives an indication of the proportion of contamination, it will be important to differentiate the use of PSA for screening and diagnostic purposes and to correct for the time period after randomization at which the contamination occurred. These are our next steps in this research effort.

PART III

RISK STRATIFICATION OF SCREEN-DETECTED PROSTATE CANCER

Chapter 7
Prevalence, treatment modalities and prognosis of familial prostate cancer in a screened population
J Urol. 2006 Apr;175(4):1332-6

Chapter 8
Metastatic disease of screen-detected prostate cancer; characteristics at diagnosis
Cancer. 2006 Dec 15;107(12):2779-85

Chapter 9
Should we replace the Gleason score with the amount of high-grade prostate cancer?
Eur Urol. 2007 Apr;51(4):931-9.

Chapter 10
Nomogram use for the prediction of indolent prostate cancer: impact on screen-detected populations
Cancer; in press

Chapter 7

Prevalence, treatment modalities and prognosis of familial prostate cancer in a screened population

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ABSTRACT

Purpose

A family history of prostate cancer is an important risk factor for this disease. The clinical presentation and prognosis of familial disease remain uncertain. In this study these entities are evaluated in the first and second rounds of a screening program in The Netherlands.

Patients & Methods

Of all men randomized in the Rotterdam section of the ERSPC, 19,970 men were eligible for screening. Information regarding the family history was obtained by a self-administered questionnaire at baseline.

Results

In the prevalence screen the cancer detection rate in 1,364 men (7.1%) with a positive family history was 7.7% (106 cancers in 1,364 screened men with a positive family history) while the positive predictive value of the biopsies was 32.2% (154 cancers of 532 biopsies). In 12,803 sporadic cases the detection rate was 4.7% and the positive predictive value was 23.6% (p 0.0001 and 0.003, RR 1.63). No clinicopathological differences were found in the 1,559 men diagnosed in the first and second rounds. The overall biochemical-free survival rate after a mean follow-up of 56.8 months (range 0 to 129.9) was 76.8%, and was not significantly different in familial and sporadic cases ($p > 0.840$). These findings were consistent for the specific treatment modalities as well.

Conclusions

Although screened men 55 to 75 years old with a father or a brother having prostate cancer themselves are at a substantially greater risk for the disease, the clinical presentation, treatment modalities and prognosis by biochemical progression are not different compared to sporadic cases.

INTRODUCTION

prostate cancer is the most frequent cancer among men older than 50 years old in Europe and the United States, accounting for respectively 225,000 and 240,000 new cases each year.[26] Epidemiological studies have shown that prostate cancer tends to affect more members of the same family than can be explained by chance alone.[128] Familial clustering of cancer was described almost a century ago, however it was not until the 1970s that genetic predisposition has been reported to have a role in the origin of cancer. Only in 1992 was the first study on the Mendelian inheritance of familial prostate cancer published. The susceptibility genes found so far explain only a fraction of the potentially inherited prostate cancer. Having a family history of prostate cancer is nonetheless regarded as the greatest risk factor for developing the disease and the genetic predisposition is possibly the strongest among all common cancers.[129] This indicates that the genetic basis of prostate cancer is more complex compared to cancer at other sites. Whether familial prostate cancer is clinically a different kind of disease than sporadic prostate cancer remains unclear. If there were a difference in prognosis between familial and sporadic prostate cancer, this would necessitate important clinical decision making. Two studies from the same American institution reported a poorer prognosis in men with familial prostate cancer,[130,131] while other American and European studies have not been able to show a difference in clinical course between familial and sporadic prostate cancer.[132-135] Little is known about PSA screening among men with a positive family history. We compared the risk of prostate cancer, the clinical and biological features at diagnosis and the prognosis of different treatment modalities for familial and sporadic prostate cancer in a screened population.

PATIENTS & METHODS

Data were collected from the screening arm of the Rotterdam section of the ERSPC. After giving written consent 21,210 of 42,376 men 55 to 74 years old were randomized into the screening arm from December 1993 through December 1999. A total of 19,970 men (94.2%) were actually screened. The participants were offered 3 screening tests of PSA measurement, digital rectal examination and TRUS. Biopsy indication was set at a PSA of 4.0 ng/mL or greater, or suspicious findings on digital rectal examination or TRUS. After November 1997 a PSA 3.0 ng/mL or greater prompted a sextant biopsy. Men were eligible for second round screening, 4 years later, if their age was younger than 75 years and if they were not diagnosed with prostate cancer in the prevalence screen. In the second screen round a PSA of 3.0 ng/mL or greater prompted a sextant biopsy. In case of a hypoechogenic lesion on TRUS a seventh, lesion directed biopsy, was taken. Clinical staging is done throughout the whole study according to the 1992 UICC TNM classification. Prostate biopsy cores are labeled and processed

individually. Biopsy results were graded by 1 uropathologist (TvdK) using the Gleason score. Information on family history was obtained by a self-administered questionnaire at baseline. There were 5,648 men who answered the family history question with "probably not". In these men 463 prostate cancers were found. All men who filled in "probably not" were excluded from this study. A positive family history was defined as having a father and/or 1 brother or more diagnosed with prostate cancer. None of the included men were first or second-degree relatives. We calculated the CDR and the RR in men with and without a positive family history. The PPV of the biopsies was calculated by dividing the number of prostate cancer found by the number of biopsies taken.

Follow-up data were obtained by reviewing patient charts every 6 months for the first 5 years following diagnosis and annually thereafter. Medical history, physical examination, dissemination studies and PSA tests were registered. Primary end point in this study was biochemical progression, which was defined as 2 consecutive PSA values of 0.2 ng/mL or higher after radical prostatectomy and 3 consecutive PSA increases (American Society for Therapeutic Radiology and Oncology definition) after radiotherapy.[80] Because no widely accepted definition for biochemical progression in watchful waiting exists, the American Society for Therapeutic Radiology and Oncology definition was arbitrarily used for follow-up of watchful waiters as well. Time of biochemical progression was backdated to the date between the first increase and the previous PSA test date. The criteria described by Collette et al were used for biochemical progression of men with metastasized disease receiving hormonal treatment (e.g. a 20% increase of the PSA over nadir, each to a value greater than 4.0 ng/mL).[81] two sided p-values were calculated using the chi-square test for grouped variables. Kaplan-Meier projection was used for biochemical progression-free survival analysis. The curves were tested for significance (p 0.05) with the log rank test. All analyses were performed with the commercially available SPSS® software version 12.0. Treatment data were based on intention to treat basis.

RESULTS

Prevalence

In round 1 of the Rotterdam section of the ERSPC, 19,970 men were screened for prostate cancer and filled in the question regarding the family history. A total of 1,364 men (6.8%) reported that 1 or more affected first degree relatives had a positive family history. In 436 cases (32.0%) this involved a brother, in 867 cases (63.6%) their father and in 61 (4.5%) a father and a brother with prostate cancer. The age of onset of the affected relative or relatives was available in 685 men (50.2%), of whom 50 (7.3%) relatives were 59 years or younger. Of all prevalence screened men with prostate cancer (1,014) 106 men reported a positive family history (10.5%). A total of

Table 7.1

		PFH[1]		NFH[3]		Total		
		N	%	N	%	N	%	***P-value***
	Screened	1,364	*6.8*	12,803	*64.1*	19,970		
Prevalence screen	**Biopsied**	329	*8.0*	2,548	*61.9*	4,117		
	PC	106	*10.5*	601	*59.3*	1,014		
	PPV		*32.2*		*23.6*		*24.6*	*0.003*
	CDR		*7.7*		*4.7*		*5.1*	*<0.0001*
	RR						*1.63*	
Round 2	**PC**	48	*8.9*	341	*62.6*	545		
Total	**PC**	154	*9.9*	942	*60.4*	1,559		
	CDR		*11.3*		*7.4*		*7.8*	*<0.0001*
	RR						*1.53*	

PFH = positive family history;
NFH = negative family history
PC = prostate cancer;
CDR = cancer detection rate;
PPV = Positive Predictive Value;
RR = Relative Risk.

4,117 men underwent biopsy and 329 (8.0%) had a positive family history. Therefore, the CDR was 7.7% and the PPV of the biopsies was 32.2%.

A negative family history was reported by 12,803 men (64.1%). In men with a negative family history, 2,548 biopsies were performed (61.9%) resulting in 601 prostate cancer diagnoses in the prevalence screen. For this group the CDR was 4.7% and the PPV of the biopsy indication was 23.6% (table 7.1). Logistic regression analysis showed that family history is an independent predictor for being diagnosed with prostate cancer (odds ratio 1.35, 95% CI 1.06 to 1.73).[136] An additional 545 cancers were found by re-screening after 4 years. In the 2 screening rounds together 1,559 men with prostate cancer were diagnosed of 19,970 men screened (CDR 7.7%, RR 1.53). The age distribution was similar for both groups (data not shown).

Demographics

The respective median age at time of prostate cancer diagnosis for positive family history and negative family history was 66.2 (mean 66.5, range 55.4 to 75.6) and 66.8 (mean 66.2, range 55.0 to 75.6), with a median follow-up of 55.4 months (mean 56.8, range 0 to 129.9). As table 2 shows, the remaining baseline characteristics of the 2 groups were well balanced. The majority of the patients had a biopsy Gleason score of 3 + 3 or less (69.9). Only 6.5% had a biopsy Gleason score of 4 + 4 or greater. The clinical tumor extension was classified as T1C (46.1%), T2 (27.7%), T3 (9.8%), T4 (0.5%). Median PSA at time of diagnosis was 5.0 (mean 8.8, range 0.6 to 315.9 ng/mL).

Table 7.2 Demographics and prognostic factors

		PFH		NFH		
		N	%	N	%	*P-value*
PC		154		942		
Screen round 1		106	*68.8*	601	*63.8*	*0.226*
Follow up (months, median)		52.0	*0-129.9*	55.4	*0-129.9*	
Age at diagnosis (years, median)		66.2	*55.4-75.6*	66.8	*55.0-75.6*	
Clinical PSA group	**<4**	49	*31.8*	325	*34.5*	
	4-10	81	*52.6*	449	*47.7*	
	>10	24	*15.6*	168	*17.8*	*0.515*
T stage	**T1C**	58	*39.2*	434	*46.9*	
	T2	68	*45.9*	355	*38.4*	
	≥T3	22	*14.9*	136	*14.7*	*0.106*
	missing	6		17		
N-stage	**N1**	1	*0.6*	10	*1.1*	*0.634*
M-stage	**M1**	2	*1.3*	6	*0.6*	*0.371*
Biopsy Gleason sum	**=<3+3**	109	*70.8*	657	*69.7*	
	7	33	*21.4*	226	*24.0*	
	>=4+4	12	*7.8*	59	*6.3*	*0.649*

PFH = positive family history

NFH = negative family history

PSA = prostate specific antigen

Table 7.3 Treatment modalities and survival

	PFH				NFH				
Treatment	**N**	**%**	**Follow-up available**	**5 yr-BFS**	**N**	**%**	**Follow-up available**	**5 yr-BFS**	***P-value***
RP	61	*39.9*	53 (86.9%)	89.8%	349	*37.7*	319 (91.4%)	86.8%	
RT	71	*46.4*	62 (87.3%)	72.2%	403	*43.6*	351 (87.1%)	77.2%	
WW	18	*11.8*	15 (83.3%)	38.7%	155	*16.8*	125 (80.6%)	67.1%	
ET	3	*2.0*	3 (100%)	56.5%	18	*1.9*	18 (100%)	38.7%	
missing	*1*				*17*				
Total	***154***		***133 (86.4%)***	***77.8%***	***942***		***813 (86.3%)***	***79.2%***	*0.487*

RP = radical prostatectomy;

RT = radiotherapy;

WW = watchful waiting;

ET = endocrine treatment

5 yr-BFS = Five year biochemical free-survival

PFH = positive family history

NFH = negative family history

Treatment modalities

The initial treatment modalities of positive vs. negative family history were 39.9% vs. 37.7% for radical prostatectomy, 46.4% vs. 43.6% for radiotherapy, 11.8% vs. 16.8% for watchful waiting and 2.0% vs. 1.9% for endocrine treatment. The numbers are shown in table 7.3. Between men with and without a family history, no differences with respect to median patient age, serum PSA level or biopsy rate were observed in the different groups of treatment.

Prognosis

Biochemical progression occurred in 166 men (10.6%) after a median follow-up time of 22.1 month (mean 25.9, range 0 to 186.2). Of those men 22 (14.3%) had a positive family history. The time from treatment to biochemical progression was median 21.9 months (mean 25.8, range

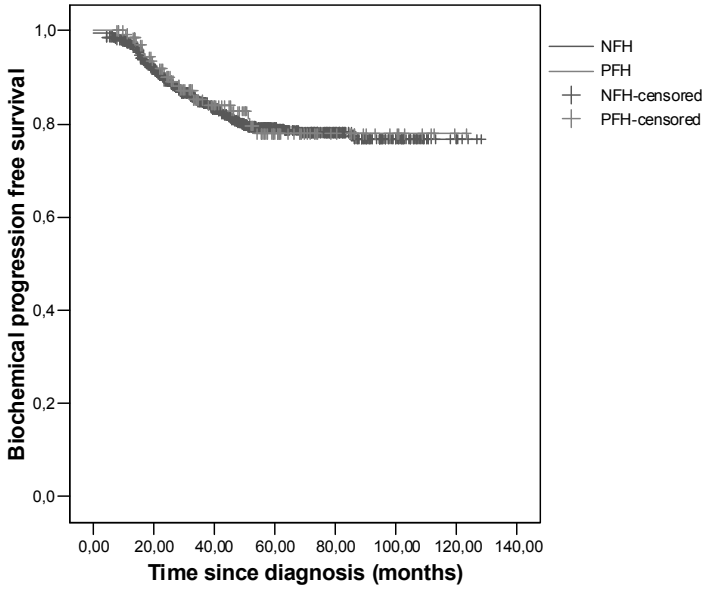

Figure 7.1 Kaplan-Meier projection of overall biochemical progression free-survival

Log-rank: P-value=0.840

Men at risk

	0	20	40	60	80	100	120	140
PFH	133	110	69	34	17	8	0	
NFH	813	660	459	263	134	49	7	0

Number of events

	0	20	40	60	80	100	120	140
PFH	0	8	18	22	22	22	22	
NFH	0	64	119	139	142	144	144	144

PFH Positive family history

NFH Negative family history

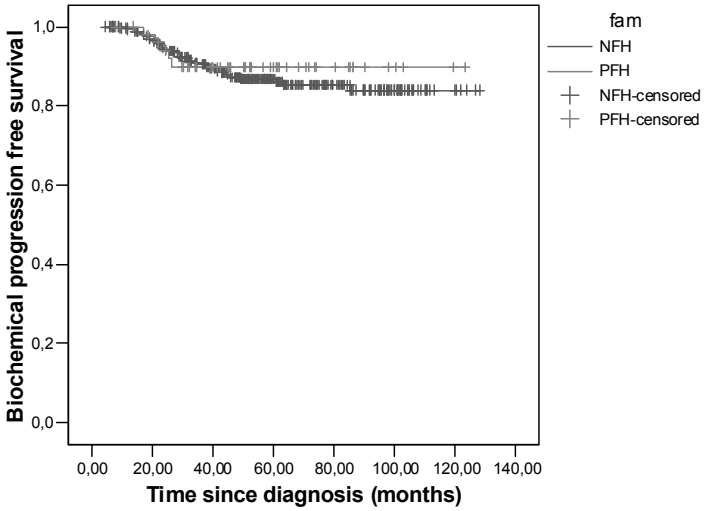

Figure 7.2 Biochemical progression free-survival in radical prostatectomy patients

Log-rank: P-value=0.584

Men at risk

	0	20	40	60	80	100	120	140
PFH	53	49	35	20	11	4	1	0
NFH	319	283	218	131	68	31	6	0

Number of events

	0	20	40	60	80	100	120	140
PFH	0	1	5	5	5	5	5	5
NFH	0	11	30	36	38	39	39	39

PFH Positive family history

NFH Negative family history

0 to 129.9) in the PFH group. In the negative family history group were 144 men (15.3%) with biochemical progression, after median 23.6 months (mean 26.9, range 10.6 to 53.3). Overall 5-year biochemical progression-free survival rates were 77.8% for positive family history and 79.2% for negative family history (Kaplan-Meier curve in figure 7.1).

After radical prostatectomy, the 5-year biochemical progression-free survival rates were 89.8% for positive family history and 86.8% for negative family history (figure 7.2).

As shown in figure 7.3 the 5-year biochemical progression-free survival rates for radiotherapy were 72.2% for positive family history and 77.2% for negative family history. Table 7.3 shows the quantity of men with biochemical progression for each individual treatment modality during total follow up. These differences were not significant.

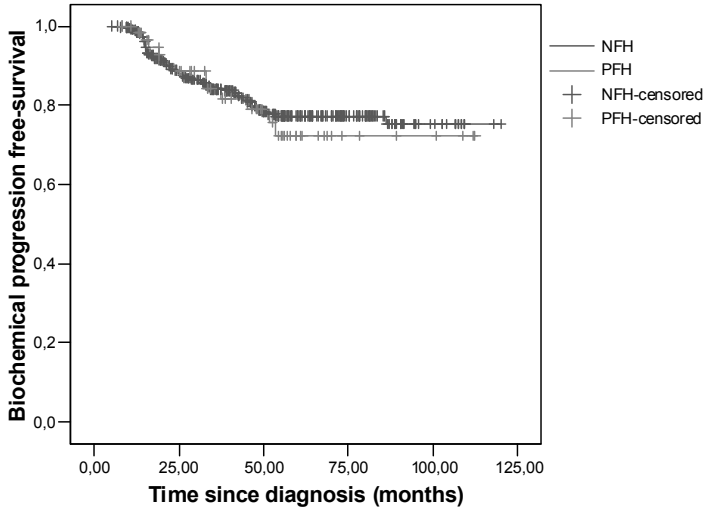

Figure 7.3 Biochemical progression free-survival in radiotherapy patients

Log-rank: P-value=0.744

Men at risk

	0	25	50	75	100	125
PFH	62	45	24	6	4	0
NFH	351	252	147	66	16	0

Number of events

	0	25	50	75	100	125
PFH	0	6	10	12	12	12
NFH	0	38	60	62	63	63

PFH Positive family history

NFH Negative family history

DISCUSSION

Prevalence

Our study provides further conformation that men with a father or a brother with prostate cancer themselves have a higher risk of developing prostate cancer (table 7.1). In the last 50 years RRs ranging from 1.3 through 18 were described.[137,138] The largest study on this topic reports on 1,922 men who were mainly diagnosed with prostate cancer before the PSA screening era.[128] When a first-degree relative had a family history of prostate cancer, the RR of being diagnosed with prostate cancer themselves was 1.60 (95% CI 1.31 to 1.97). In our study the RR was 1.53, which is lower than in most other reports.[136] However, most of those studies are case-control studies, which are subject to various kinds of bias. Therefore, the true RR is probably somewhat lower than in most studies. We only included men 55 through 75 years old. That means the RR we found might give an underestimation of the actual risk because

the influence of the family history is more explicit at a younger age, which is referred to as prostate cancer of early onset.[139]

The proportion of patients with a positive family history was 10.5% of all men diagnosed with prostate cancer in the prevalence screen. In the literature these percentages range from 11.1% through 18%.[140,141] Our relatively small number of positive family histories may have been a result of the different selection criteria for familial prostate cancer we used. It may also have been underestimated because the "probably not" group contained some men with a positive family history. A second explanation for the higher proportion found in the literature could be that men who have patients with prostate cancer in their proximity, often being a father or a brother, are more aware of the disease and its screening possibilities.

Whether the use of a self-administered questionnaire at baseline is a reliable method of acquiring data on family history is debatable. Family history was self-reported before screening started, and is believed to be fairly accurate and reliable, as has been shown by Zhu et al.[142]

Demographics

The clinical presentation of familial prostate cancer remains controversial. As this screening round was a prevalence screen, we should, like Gronberg et al, have been able to show differences in the tumor grade and frequencies of advanced disease between familial and sporadic cases.[143] However, no such observations were made in our study, nor in other reports.[130,132,134,135,140] Our findings of clinicopathological similarity (initial PSA, T stage and Gleason score) of both groups are consistent with those reports.

Although other studies have shown a significant lower age at diagnosis in men with a positive family history, we found no difference.[133,144] Only 2 studies have reported findings similar to those in our study.[132,137] Azzouzi et al postulated that this difference was due to selection bias, because only men treated with radical prostatectomy were described.[132] The findings of Makinen et al and our findings are probably biased by selection of an age grouping which excludes men younger than 55 years.[137] Among men with early onset prostate cancer, hereditary susceptibility is much more common, and may cause up to a third of cases diagnosed before age 60 years and almost half of those in men 55 years or younger.[139] There are just a few studies that reported on familial prostate cancer in a screen setting. The report by Makinen et al describes the familial influence in the Finnish part of the ERSPC study. Their screen algorithm is quite similar to ours except for the PSA threshold value and the screen age, which is 55 to 70 years. In Rotterdam men are screened until they are 75 years old. Makinen et al used a threshold value of 4.0 ng/mL as a biopsy indication,[137] while ours was 4.0 ng/mL at the start of the study but changed to 3.0 ng/mL in November 1997. Since the authors showed that age at diagnosis did not statistically differ between a positive and a negative family history, a similar

age at diagnosis could well be a screen effect. Men having a close relative diagnosed with prostate cancer may also have a higher familial awareness of prostate cancer and, therefore, have a higher sense of urgency about getting screened. In this study men with positive and negative family history were screened in a similar way, thereby excluding the possible bias of familial awareness. The similarity in age at diagnosis is not due to a difference in age distribution in the recruited population, as this distribution was similar in participants irrespective of family history (data not shown). Although most men with early onset prostate cancer have been described as having a positive family history,[139] the age distribution in our study was similar in both groups. It is possible that those younger men were not included in our study, because they had been diagnosed with prostate cancer before screening started. This would have caused us to overestimate the median age at diagnosis, which would also explain our relatively low proportion of men with a positive family history. In terms of treatment, if one considers the similar distribution of treatment modalities in both groups, knowledge of family history did not determine the choice of initial treatment.

Prognosis

In this study screen detected prostate cancer did not show a significant difference in overall biochemical progression-free survival between the positive and the negative family history group (figure 7.1). Therefore, we confirm the results of most reports on the follow-up of familial prostate cancer, except for those by Kupelian et al,4,5 which both show a worse prognosis for hereditary prostate cancer. We have no clear explanation for this difference other than the strictness of selection criteria used for familial and hereditary prostate cancer. This has been defined by Carter et al as the presence of prostate cancer in at least 3 first-degree relatives, in 3 consecutive generations, or in 2 first-degree relatives with an age of onset less than 55 years.[144] Thus, hereditary prostate cancer is actually a subset of our population of familial prostate cancer, which was defined as the existence of a father and/or 1 brother or more with the disease. Contrasting the findings of Kupelian et al, Bova et al found that the prognosis of familial prostate cancer after radical prostatectomy is not different from that in men without a history of this disease.[134] Patients receiving definitive radiation therapy for localized prostate cancer were described by Ray et al, who did not find a relationship between positive first-degree family history of prostate cancer and biochemical progression-free survival rates.[141] Our data are uniform with these findings.

Although biochemical progression-free survival cannot be considered as a definitive end point for prostate cancer prognosis, it is supposed to be the best indicator for prostate cancer specific survival. Longer follow-up than ours of mean 56.9 months is mandatory for evaluation of (disease specific) mortality.

CONCLUSIONS

In this evaluation of the first and second screen round of the ERSPC we have shown that men with a positive family history of prostate cancer are at a substantially greater risk of being diagnosed with the disease. However, the clinicopathological features of these patients age 55 to 75 years old are not different and patients are treated in the same way as those with sporadic prostate cancer. Moreover, screen detected familial related prostate cancers have no significantly different prognosis, by the biochemical progression-free survival rates than those diagnosed in screened men without a family history of the disease. Whether overall mortality will be equal in both groups remains unclear until longer follow-up is available.

Chapter 8

Metastatic disease of screen-detected prostate cancer; characteristics at diagnosis

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ABSTRACT

Backgrounds

Screening for prostate cancer has not only led to a stage migration, but also to a higher incidence of the disease. A decrease in mortality has occurred in several countries during the same time period. Risk stratification of screen-detected cancers at diagnosis has become more important for the anticipation and interpretation of changing incidence-mortality ratios.

Patients & Methods

From 1993 to 1998, 633 men were diagnosed with non-metastatic prostate cancer in the prevalence screen of the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC). The characteristics at diagnosis of men who developed metastatic disease were compared to men without evidence of metastases during follow-up.

Results

During the median follow-up of 7.5 years, 41 men developed metastatic disease. After 10 years the metastasis-free survival rate was 89.6%, the overall survival 64.7%. In a Cox-model 2logPSA, biopsy Gleason score and the number of biopsy cores with prostate cancer were independent predictors for the development of metastases; the latter only predicted metastases that presented within 60 months of follow-up.

Conclusion

The metastasis-free survival of men with prostate cancer detected in our prevalence screening was very high. Whether this was related to the beneficial effects of screening or to overdiagnosis due to screening (or both) remains unclear. The prognostic factors known for clinically diagnosed disease also hold for screen-detected disease.

INTRODUCTION

Prostate cancer is an important burden of health in the western world; it accounts for approximately 3% of all deaths in the US.[33] Since prostate-specific antigen (PSA) became available in the late 1980s, it has not only been used for diagnostic and follow-up purposes but increasingly for screening practices as well. Age-adjusted incidence rates increased over the past several decades, with dramatic increases associated with the widespread use of prostate-specific antigen (PSA) screening in the late 1980s and early 1990s, followed by a more recent fall in incidence. Age-adjusted mortality rates have recently paralleled incidence rates with an increase followed by a decrease in the early 1990s.[32] However, whether this decrease in mortality is the result of screening efforts or of improvements in treatment modalities remains a matter for debate. As a result of the increase in incidence and the decrease in mortality, the number of men diagnosed with prostate cancer per prostate cancer death (i.e. the incidence-mortality ratio) has increased accordingly. Between 1989 and 2002, for example, the incidence-mortality ratio increased by 61.5% in the US (reaching 6.3 diagnosed men per prostate cancer death),[32] and has recently increased to 7.8.[33] In the Netherlands it increased by 53.1% (reaching 3.0 diagnosed men per prostate cancer death in 2002).[73] A mathematical model based on data from the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC) has shown that in a population-based screening program with a four-year screen interval for men aged 55 to 75 years, 54% (95% CI: 51–59) of cases would not have been diagnosed in PSA test absence.[37] By definition, these cancers are overdiagnosed, which tends to be followed by overtreatment, and the associated toxicity of the different prostate cancer treatment modalities.[145,146]

Due to this burden of overdiagnosis and its ethical and economical consequences, the need for risk stratification of prostate cancer patients has become increasingly important. In screening trials, it is still poorly understood which cancers deserve treatment and which do not. On the other extreme, it is important to identify those cancers which are at high risk for the development of prostate cancer metastases and prostate cancer death despite treatment.[147] In screening trials, a reduction in prostate cancer deaths may be obtained by the detection (and subsequent treatment) of poorly differentiated cancers in their localized or regional stage of disease before they have metastasized. On the other hand, some cases diagnosed with prostate cancer may still develop metastases despite screening efforts. If it were possible to identify these cases on the moment of diagnosis, a more intensified or aggressive therapeutic approach could be chosen.

This report contributes to the extreme side of the risk spectrum: the predictors of metastatic disease. There are only limited survival data available of men with screen-detected prostate cancer. Therefore, we studied the prognostic factors related to the development of metastases in men with screen-detected non-metastatic prostate cancer at diagnosis.

PATIENTS & METHODS

The European Randomized study of Screening for Prostate cancer (ERSPC) was designed to investigate the feasibility of screening for prostate cancer. The primary goal of the ERSPC is to show if a 25 % prostate cancer specific mortality reduction can be achieved by early detection at the 5% significance level with a power of 80%. Therefore, 267,994 men in eight European countries were randomized. From 1993 to 1999, in Rotterdam alone 42,376 men aged 55-74 were randomized between the screening (n=21,210) and the control-arm (n=21,166) of the ERSPC. The details of the Rotterdam section of the ERSPC are described elsewhere.[78] In short, men in the screen arm were offered a biopsy according to two subsequent protocols. The first one was applied from December 1993 to April 1997: in this protocol (protocol I) a biopsy was prompted by a suspicious digital rectal examination (DRE), transrectal ultrasound (TRUS) and/or a PSA ≥ 4.0 ng/mL. From May 1997, the protocol was changed and all men with a PSA ≥ 3.0 ng/mL were offered a biopsy, regardless of the findings on DRE and TRUS (protocol II). A standardized, lateralized sextant biopsy was performed throughout the whole study.[83] If a hypo-echogenic lesion was evident on TRUS, a seventh lesion directed biopsy was taken. All biopsy cores were processed individually, examined and scored according to Gleason by one uro-pathologist (T.H.v.d.K.).

Study group

All men diagnosed with non-metastatic prostate cancer during their first screening visit in the first four years of ERSPC screening (before January 1st 1998) were selected (N=633; CONSORT diagram figure 8.1). Nine men (1.4%) were excluded because they had metastatic disease at time of diagnosis. No comparisons with the control-group of the ERSPC were made, because of the close relationship of the used endpoint with the primary endpoint of the ERSPC (i.e. prostate cancer-mortality). Furthermore, the prognostic factors of the control arm of the study are incomplete, as data-acquisition is still ongoing.

Endpoint

The primary endpoint for this analysis was the occurrence of metastatic disease on follow-up. The secondary endpoint was overall survival.

Within ERSPC, an independent committee performs the review of deceased cases. Three reviewers (a surgeon, a urologist and a medical epidemiologist) separately judged the anonymized patient charts without knowledge of randomization arm. The methods described by De Koning et al. are used for judgment of metastatic disease as well.[148] Additionally, all men with a PSA of 150 ng/mL or more at diagnosis or during follow-up were assumed to have metastatic disease.

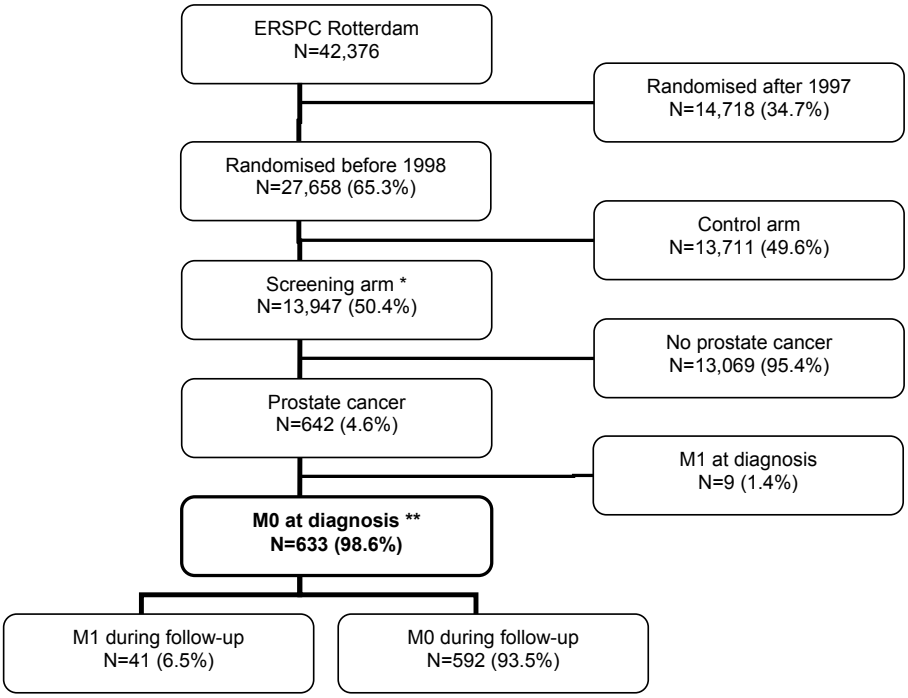

Figure 8.1 CONSORT diagram

* 10.456 men (75.0%) were screened by protocol I and 3.491 (25.0%) by protocol II.

** 466 men (73.6%) were diagnosed by protocol I and 167 (26.4%) by protocol II.

Protocol I (December 1993-April 1997)

Biopsy prompted by:

1. Suspicious digital rectal examination (DRE)
2. Suspicious transrectal ultrasound (TRUS)
3. PSA >= 4.0 ng/mL

Protocol II (April 1997-January 1998)

Biopsy prompted by:

PSA >= 3.0 ng/mL

Statistics

Significant risk factors for time from diagnosis to prostate cancer metastases were examined using log-rank survivorship analysis and Cox proportional hazards regression. Separate univariate (log rank test) and multivariate (Cox proportional hazards model) failure time analyses using metastatic disease as an endpoint were performed. A Cox proportional hazards model was used with $P<.20$ determining which variables should be entered into the model at each step. The proportional hazards assumption of the Cox model was tested through the graphical examination of the log-log survival plots for each of the variables in the model. These plots formed approximate parallel straight lines as required. All statistical analyses were performed using SPSS 12.0.1 (SPSS Inc., Chicago, IL), and $P<.05$ was considered statistically significant.

RESULTS

From December 1993 to January 1998, 633 men were diagnosed with non-metastatic prostate cancer in the Rotterdam section of the ERSPC. During the mean (SD) and median (range) follow-up times of 7.1 (2.2) and 7.5 years (0.2-12.0) 41 men (6.5%) were diagnosed with metastatic disease. Table 8.1 shows the characteristics of men with prostate cancer who did and who did not develop metastatic disease on follow-up at baseline. The ten year metastatic-free survival was 89.6% (figure 8.2). The mean time period from diagnosis until metastatic disease was 62.4 months (median 58.7, range 13.7-110.3). After 10 years the overall survival was 64.7%. The time to metastases as a function of the significant prognostic factors Gleason score and initial PSA at diagnosis in the univariate analysis (log rank test) is graphically depicted in the Kaplan-Meier graphs of figure 8.3 and 8.4. The outcome of the different treatment modalities is shown in figure 8.5. PSA-level at diagnosis, biopsy Gleason score, clinical stage, the number of biopsy cores that were invaded with cancer and the applied treatment were significant predictors of metastatic disease in the univariate analysis (table 8.1).

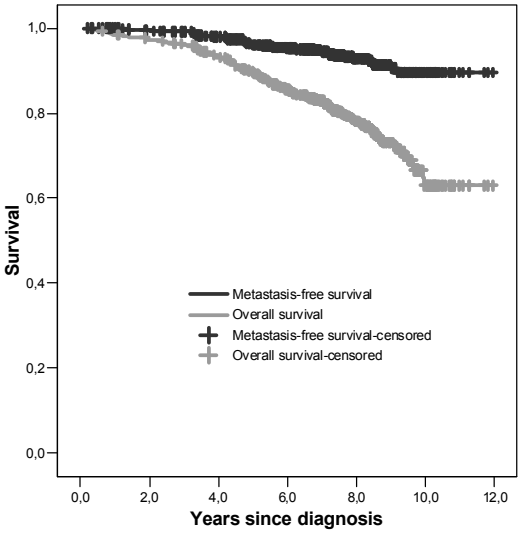

Figure 8.2 Kaplan-Meier projection of overall-survival and metastatic free survival (N=633)

Men at risk

Year	*0*	*2*	*4*	*6*	*8*	*10*
Overall survival	633	612	574	485	255	36
%	*100*	*97.3*	*93.6*	*85.9*	*78.4*	*64.7*
Survival free of M+	633	610	570	481	254	35
%	*100*	*99.4*	*98.0*	*95.5*	*92.9*	*89.6*

Log-rank test: P-value<0.001

Table 8.1 Characteristics at baseline of 633 men with no evidence of metastasis at diagnosis

		Men with metastatic disease during follow-up (M1)	Men without metastatic disease during follow-up (M0)	Total	*P-value*
Patients	*No. (%)*	41 (6.5)	592 (93.5)	**633**	
Age (years)	*Mean (median; min-max)*	67.3 (67.8 ; 56.4-75.0)	66.0 (66.7; 55.0-75.5)	**66.1 (66.7; 55.0-75.5)**	*0.14 ***
PSA (ng/ml)	*Mean (median; min-max)*	17.9 (12.7; 2.7-62.9)	8.6 (5.6 ; 0.3-145.0)	**9.2 (5.7; 0.3-145.0)**	*<0.001 ***
	≤3.0 (%)	1 (2.4)	89 (15.0)	**90 (14.2)**	*<0.001 **
	3.1-10.0 (%)	16 (39.0)	382 (64.5)	**398 (62.9)**	
	10.1-20.0 (%)	11 (26.8)	84 (14.2)	**95 (15.0)**	
	≥20.1 (%)	13 (31.7)	37 (6.3)	**50 (7.9)**	
Clinical stage	*T1C (%)*	4 (9.8)	162 (27.4)	**166 (26.2)**	*<0.001 **
	T2 (%)	15 (36.6)	302 (51.0)	**317 (50.1)**	
	T3/4 (%)	22 (53.7)	128 (21.6)	**150 (23.7)**	
Biopsy Gleason	*<7 (%)*	10 (24.4)	396 (66.9)	**406 (64.1)**	*<0.001 **
	7 (%)	16 (39.0)	156 (26.4)	**172 (27.2)**	
	>7 (%)	15 (36.6)	40 (6.8)	**55 (8.7)**	
Number of cores invaded with prostate cancer	*1-2 (%)*	8 (19.5)	298 (50.3)	**306 (48.3)**	*<0.001 **
	3-4 (%)	11 (26.9)	203 (34.3)	**214 (33.8)**	
	5-6 (%)	14 (34.1)	76 (12.8)	**90 (14.2)**	
	7 (%)	8 (19.5)	15 (2.5)	**23 (3.6)**	
Prostatic volume (cc)	*Mean (median; min-max)*	41.6 (37.9; 20.4-92.5)	40.0 (35.1; 13.4-125.2)	**40.1 (35.1; 13.4-125.2)**	*0.26 ***
Treatment	*RP (%)*	5 (12.2)	227 (38.3)	**233 (36.8)**	*<0.001*
	RT (%)	35 (85.4)	299 (50.5)	**334 (52.8)**	
	WW (%)	0 (0.0)	59 (10.0)	**59 (9.3)**	
	ET (%)	1 (2.4)	7 (1.2)	**7 (1.1)**	
Risk-group[13]	*1 (%)*	1 (2.4)	77 (13.0)	**78 (12.3)**	*<0.001*
	2 (%)	27 (65.9)	485 (81.9)	**512 (80.9)**	
	3 (%)	13 (31.7)	30 (5.1)	**43 (6.8)**	
Follow-up (years)	*Mean (median; min-max)*	5.2 (4.9; 1.1-9.2)	7.3 (7.6; 0.2-12.0)	**7.1 (7.5; 0.2-12.0)**	

P-values were calculated for men with versus men without metastatic disease

* *Chi-square test*

** *Mann Whitney U test*

RP *Radical prostatectomy*

RT *Radiotherapy*

WW *Watchful waiting*

ET *Endocrine therapy*

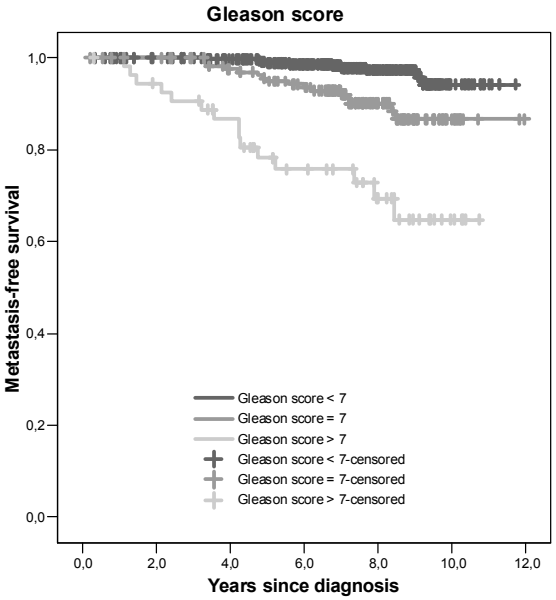

Figure 8.3 Kaplan-Meier projection of the metastatic-free survival by biopsy Gleason score groups (N=633).

Men at risk

Year	*0*	*2*	*4*	*6*	*8*	*10*
Gleason score < 7	406	393	372	310	162	17
Gleason score = 7	172	168	153	135	65	12
Gleason score > 7	55	50	42	30	18	5

Log-rank test: P-value<0.001

Two hundred thirty two men (36.3%) elected radical prostatectomy; 5 (2.2%) developed metastatic disease. The 10-year metastasis-free survival was 97.7%. The mean time period from diagnosis to metastatic disease was 48.2 months (median 46.3; range 38.8-59.1). After 334 radiotherapy treatments (52.8%), 35 men (10.5%) developed metastases; after a median time period of 62.6 months (mean 64.5; range 13.7-110.3).

Only one man was diagnosed with metastatic disease after hormonal treatment was applied. The nine men who had metastatic disease at diagnosis all received hormonal treatment; those were excluded from our analysis. In the watchful waiting group no one developed metastatic disease.

Regression models

In a multivariate model, the time to failure in radical prostatectomy patients is significantly related to the initial PSA level. Metastases occur earlier in time during the follow-up if the initial PSA is higher. A Cox proportional hazards model can describe this observation quantitatively (hazard ratio for 2log initial PSA = 3.2; 95% C.I. 1.4 – 7.4). In radiotherapy patients the group

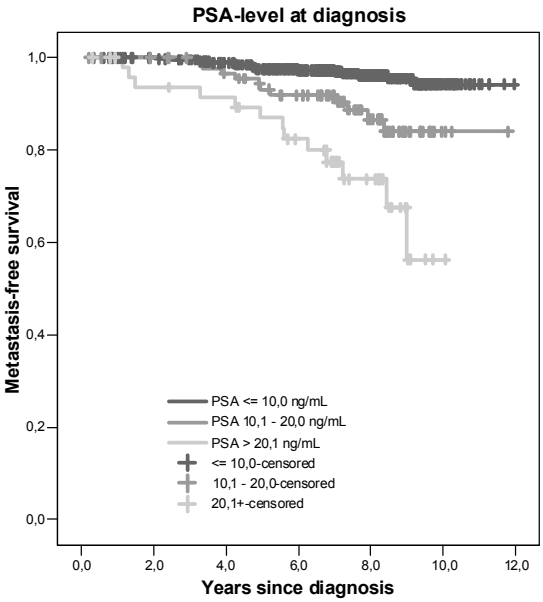

Figure 8.4 Kaplan-Meier projection of the metastatic-free survival by PSA groups.

Men at risk

Year	*0*	*2*	*4*	*6*	*8*	*10*
PSA ≤ 10.0	488	475	440	368	188	30
PSA 10.1-20.0	95	92	85	73	40	3
PSA > 20.0	50	44	42	34	17	1

Log-rank test: P-value<0.001

with a Gleason score ≥ 8 and, jointly, a total number of biopsy cores positive for cancer of 6 or possible 7 clearly showed a different failure pattern when compared to the rest of the radiotherapy patients. In the former group the metastases occurred between 23 and 51 months. In the remaining patients 2logPSA and a Gleason sum ≥ 8 predict the time to metastasis in a Cox proportional hazard model. A way to model both observations jointly is to assume that the predictive potential of the total number of biopsy cores with prostate cancer and the biopsy Gleason score strongly affects the time to metastasis during the first 60 months of the follow-up. After that time period the predictive potential of the number of biopsy cores with prostate cancer decreases strongly and the initial PSA level and poorly differentiated tumors remain the only predictors. The hazard ratio for the time varying covariate condition described by [Gleason score ≥ 8 & number of biopsy cores with prostate cancer ≥ 6 and follow-up time less than 60 months] equaled 71 (18-288), the hazard ratios for 2log transformed initial PSA and Gleason score ≥ 8 equaled 1.6 (1.3 – 2.0) and 2.5 (1.1 – 5.7) respectively.

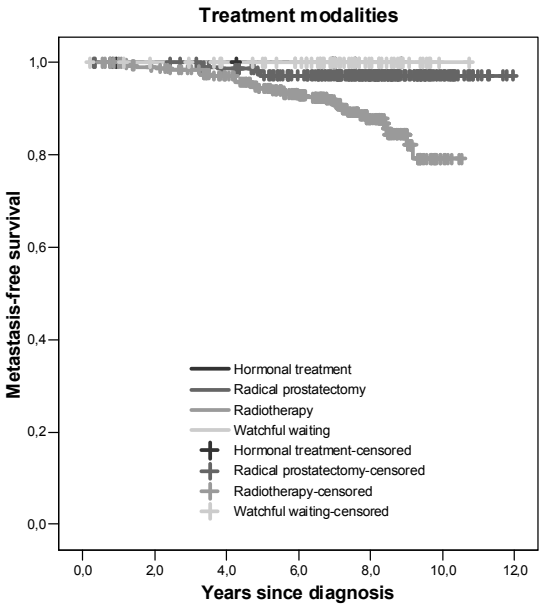

Figure 8.5 Kaplan-Meier projection of the metastatic-free survival of the different treatment modalities

Men at risk

Year	0	2	4	6	8	10
Hormonal treatment	7	7	7	5	1	0
Radical Prostatectomy	233	229	219	192	121	27
Radiotherapy	334	320	290	232	103	6
Watchful waiting	59	56	52	46	20	1

Log-rank test: P-value<0.001

DISCUSSION

Screening leads to the detection of a large number of prostate cancers. Most of these cancers are expected to have beneficial prognostic features compared to non-screened populations, with lower grades and lower stages of disease. Still, some men in the screened group will decease from the consequences of prostate cancer during follow-up. In the present study, 41/633 (6.5%) of all diagnosed cases with prostate cancer developed metastatic disease during the median follow-up period of 7.5 years. In the whole cohort of patients diagnosed with prostate cancer, the 10 year metastasis-free survival was 89.6%, which contrasted sharply with the overall survival of 64.7%. In the radical prostatectomy patients very few men developed metastases; the time to metastases was significantly related to the initial PSA level. In the radiotherapy patients the 2log transformed PSA-level at diagnosis, the number of biopsy cores with prostate cancer and the biopsy Gleason score were identified as individual predictors for the development of metastases during the first sixty months of follow-up. Thereafter, the

predictive value of the number of biopsy cores with prostate cancer decreased, while the Gleason score and the 2logPSA remained predictive for metastases.

Men detected in the prevalence screening round of the Rotterdam section of the ERSPC had a high metastasis-free survival. Two factors could explain this low rate of occurrence of prostate cancer metastases compared to pre-screened populations: (1) overdiagnosis and (2) downstaging and downgrading. The advent of screening has been the major reason for the increased incidence of prostate cancer over the last decades.[33] The overdiagnosis which is caused by a systematic screening program like ours can only be expected to be larger.

In our study most patients developed metastases after radiotherapy. The characteristics at baseline indicate that more high risk patients were treated by radiotherapy. A retrospective analysis of radical prostatectomy versus radiotherapy, with a correction for the prognostic factors, has not been performed, because of its limited value in this non randomized setting. This study provides no proof of the effectiveness of the treatment modalities under study. In order to compare the oncological outcome of radical prostatectomy and radiotherapy in screen-detected disease, the results of randomized studies like the ProtecT study have to be awaited.[149]

Another reason for the poorer performance of men treated with radiotherapy is that most of the patients in current studies which have comparable oncological results as radical prostatectomy series were irradiated with 72 Gray or more. During the past 5 years, there have been two major breakthroughs in the use of external-beam radiotherapy for early prostate cancer: dose escalation and the use of adjuvant hormone therapy. These new applications are based on evidence from prospective clinical trials with superior methods. A prospective randomized trial, in which a conventional dose of 70 Gray was compared with a dose escalation to 78 Gray showed a significant survival benefit for intermediate and high risk patients.[150] In our population, only 8.0% of men treated with external beam radiotherapy received 72 Gray or more; the remainder received less. The majority of men with metastatic disease have been irradiated with 66 or 68 Gray.

It is interesting to note that the subgroup of patients with metastases after 60 months of follow-up is absent in the radical prostatectomy group of patients. This may reflect that patients with favorable prognostic factors were preferably treated by radical prostatectomy. Although the follow-up period was similar for radical prostatectomy and radiotherapy, the time to diagnosis of metastases was different. After radical prostatectomy, metastases developed after a maximum duration of 59.1 months. This contrasts with the last event after radiotherapy, which occurred 110.3 months after diagnosis. The multivariate analysis clearly showed that radiotherapy patients with a Gleason score ≥ 8 and, jointly, a total number of biopsy cores of 6 or 7 with cancer, had a different failure pattern when compared to the rest of the radiotherapy patients. In the former group the metastases occurred between 23 and 51 months. Remarkably, however, 5 patients with the same condition did not develop metastases so far (median follow-up time of these patients, 95 months; range 23-121).

The majority of men who developed metastases were treated with curative intent, namely radiotherapy or radical prostatectomy alone. In these cases the curative treatment was clearly not sufficient to prevent the disease from developing metastases. Another explanation could be that these men already had tumor spread outside of the prostate at diagnosis. Therefore, these men would likely have been candidates for adjuvant treatment or should have been enrolled in early aggressive treatment trials. In men who developed metastatic disease in our series despite surgery or external beam radiotherapy alone, clearly the treatment applied was not aggressive enough.

CONCLUSION

Metastatic prostate cancer is relatively rare in men with screen-detected prostate cancer. It is not known to what extent this results from dilution by overdiagnosed cancers, and to what extent to treatment or screening. The individual risk factors for the development of metastases include 2logPSA, the biopsy Gleason score and the number of biopsy cores with prostate cancer. The latter loses its predictive value 60 months after diagnosis in our study. These data can serve as useful guidelines for the identification of patients who are in need of aggressive treatment. Furthermore, these prognostic factors predict with reasonable accuracy in which men the development of metastatic disease is less likely and which can therefore be considered for local treatments and for active surveillance strategies.

Chapter 9

Should we replace the Gleason score with the amount of high-grade prostate cancer?

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ABSTRACT

Objectives

The stage and grade shift of diagnosed prostate cancer has led to a diminished prognostic power of the Gleason score system. We investigated the predictive value of the amount of high-grade cancer (Gleason growth patterns 4/5) in the biopsy for prostate-specific antigen (PSA) and clinical relapse after radical prostatectomy.

Patients & Methods

PSA-tested participants (N = 281) of the European Randomized Study of Screening for Prostate Cancer (ERSPC) who underwent radical prostatectomy were analyzed. Besides clinical features, and serum-PSA, histopathologic features as determined in the diagnostic biopsy and matching radical prostatectomy specimen were related to patient outcome.

Results

At a median follow-up of 7 yr, 39 (13.9%), 24 (8.5%), and 12 (4.3%) patients had PSA ≥0.1 ng/mL, PSA ≥1.0 ng/mL, and clinical relapse after radical prostatectomy, respectively. Using Cox proportional hazards, PSA level ($p = 0.002$), length of tumor ($p = 0.040$), and length of high-grade cancer ($p = 0.006$) in the biopsy, but not Gleason score, were independent prognostic factors for biochemical relapse (PSA ≥0.1 ng/mL) when assessed as continuous variables. In radical prostatectomies, the proportion of high-grade cancer ($p < 0.001$) was most predictive of relapse (PSA ≥0.1 ng/mL). For PSA ≥1.0 ng/mL and clinical relapse, the amount of high-grade cancer, both in the biopsy specimen ($p = 0.016$ and $p = 0.004$, respectively) and radical prostatectomy specimen ($p = 0.002$ and $p = 0.005$, respectively), but not Gleason score, was an independent predictor.

Conclusions

In biopsy and radical prostatectomy specimens of surgically treated prostate cancer, the amount of high-grade cancer is superior to the Gleason grading system in predicting patient outcome. We propose that, in addition to the Gleason score, the amount of Gleason growth patterns 4/5 in the biopsy (whether absolute length or proportion) should be mentioned in the pathology report.

INTRODUCTION

The histologic differentiation grade is the strongest prognosticator of prostate cancer. Different histologic grading systems for prostate cancer have been developed historically, and the Gleason grading system and for prostate cancer is now being used most widely.[84,151] This system is preferred over other grading systems such as those of the World Health Organization (WHO), and the MD Anderson Cancer Center (Houston, TX) grading system because it accounts for the remarkable heterogeneity of prostate cancer by identifying five different growth patterns from 1 (most differentiated) to 5 (least differentiated).[104,152] By adding the most dominant growth pattern (the primary Gleason pattern) to the next most dominant growth pattern (the secondary Gleason pattern) a 9-tiered total score of ascending aggressiveness from 2 to 10 is obtained.

A weakness in the Gleason grading system is that growth patterns that do not constitute the primary or secondary patterns (i.e., the tertiary growth patterns) are not reflected in the total score.[153] To deal with this issue, the International Society of Urological Pathology (ISUP) group recommended that in presence of three different growth patterns on the needle biopsy, both the primary pattern and the highest grade should be recorded.[154] It is hypothesized by some that the biologic behavior of a tumor is directly related to the presence and amount of poorly differentiated components within the tumour.[155,156] For this reason, it was advised to mention the presence of even small foci of high-grade cancer in the pathology report.[157,158] Stamey and colleagues have even argued that we should move away from the Gleason scoring system and simply estimate the percentage of high-grade cancer in the radical prostatectomy specimen.[155]

In counseling patients with prostate cancer about their choice for local treatment alone, for combined modality treatment, or for active surveillance, an accurate risk assessment at the time of diagnosis is warranted. Therefore, provision of all clinically relevant prognostic information is needed to guide clinical decision-making.[159] This is one of the few studies that we know of that correlates the amount of high-grade cancer in the diagnostic biopsy, and in the radical prostatectomy specimen, with biochemical and clinical recurrence rates after radical prostatectomy.

PATIENTS & METHODS

Patients

The study group consisted of 281 consecutive men who underwent radical prostatectomy at the Erasmus Medical Center Rotterdam between June 1994 and December 1999. Mean

age was 64 yr (range: 55–73), and median prostate-specific antigen (PSA) level was 5.2 ng/mL (range: 0.8–29.5 ng/mL). All men were participants in the screening arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC).[101] A biopsy was prompted when the PSA level was ≥3.0 ng/mL or when digital rectal examination (DRE) was suspicious for cancer at low PSA values (0.0–2.9 ng/mL). The biopsy procedure consisted of a systematic lateralized sextant biopsy.[160] The decision to perform radical prostatectomy was made by the patient and his urologist with consideration of the patient's age, comorbidities, biopsy tumor features, and personal preferences. All patients underwent pelvic lymph node dissection prior to radical prostatectomy, and none received hormonal treatment or transurethral resection for benign disease prior to operation.

Follow-up

Patients were followed with serial PSA measurements at 3-mo intervals for the first year after radical prostatectomy, semiannually for the second year, and yearly thereafter. Two definitions for PSA relapse were used. The first definition was two sequential detectable PSA levels ≥0.1 ng/mL, and the second definition demanded that serum PSA had to reach a level of 1.0 ng/mL at least. This latter definition was chosen to identify those who are believed to be at risk of clinical disease progression. Time to biochemical progression was defined as the time from radical prostatectomy to the time of PSA relapse, or until last follow-up, if the patient did not have a relapse. For those with PSA relapse after radical prostatectomy, DRE was performed to assess whether there was local disease progression. Local relapse was defined as recurrence of disease as proven by a positive result for cancer histology near the vesicourethral anastomosis. Metastatic disease was indicated by hotspots on bone scintigraphy or lesions suspicious for cancer on abdominal computed tomography. Time to clinical progression was defined as the time from radical prostatectomy to the time of first recording of clinical recurrence or to date of last follow-up if the subject did not have a relapse. No patient received adjuvant hormonal or radiation therapy, until disease progression occurred.

Pathologic evaluation

All sextant diagnostic biopsy cores were labeled and processed separately. The biopsy cores were inked at their capsular ends, fixed in 10% buffered formalin, embedded in paraffin, freshly cut into 4-µm tissue sections, and mounted on glass slides. Haematoxylin and eosin slides of three subsequent levels of the biopsy cores were histologically examined, the length (in millimeters) of each separate core was measured, and a total Gleason score of the biopsy sextant was assigned by a specialized genitourinary pathologist (TvdK). The number of cores positive for cancer was assessed. Each biopsy core was schematically divided into 10 parts, and presence of low-grade (Gleason growth patterns 1–3) and high-grade (Gleason growth pattern 4/5) cancer was determined. Using the length of the biopsy cores, the length of tumor (in millimeters) could be assessed for each biopsy core and for the biopsy sextant, as was the

length (in millimeters) of high-grade cancer. Subsequently, biopsy tumor involvement (the percentage of the biopsy specimen involved with cancer) was determined, as was high-grade tumor involvement (the percentage of the cancer that had high-grade components).

Radical prostatectomy specimens were fixed, embedded, and processed according to well-established protocols.[161,162] A global prostatectomy Gleason score was determined, and the tumor was staged according to the TNM 1997. The proportion of the tumor consisting of high-grade cancer was evaluated on an incremental scale from 0% to 100%. All tumor areas were traced and outlined on the slides, and subsequent morphometric analysis was performed to determine tumor volume.[163] Presence of tumor cells at the inked margin of resection was considered a positive surgical margin.

Statistical analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS 12.0; SPSS, Chicago, IL). Spearman rank correlations were used to determine the correlation between clinical and histopathologic variables as assessed in the biopsy specimen and those in the radical prostatectomy specimen. Cox proportional regression analysis was used to assess the relationship between preoperative or postoperative variables and PSA relapse (≥0.1 ng/mL, ≥1.0 ng/mL) or clinical relapse after radical prostatectomy. Preoperative variables were used as continuous variables in the models except for biopsy Gleason score and clinical tumor stage (table 9.2 and table 9.3). Subsequently, analyses were also performed when Gleason score 7 cancers were divided into 3+4 and 4+3 subcategories. Postoperative variables such as percentage of high-grade cancer and tumor volume were used as continuous variables; others were used as categorical variable (Gleason score) or dichotomized (extraprostatic extension, invasion into adjacent organs, surgical margins). For all Cox regression multivariable analyses the assumptions were tested and met. Kaplan-Meier curves were constructed to show the probability of remaining free of PSA relapse and clinical progression as a function of time after radical prostatectomy. The assumption that no predictive value existed for the variable evaluated was rejected if $p < 0.05$. To identify independent prognostic factors, backward stepwise Cox regression analysis was performed by removing variables from the model that were not statistically significant at the univariate level, while controlling for other variables. Forward stepwise elimination was performed to verify that the same parameters remained of prognostic significance in the final models.

RESULTS

Patients

Median follow-up for the cohort of 281 patients was 81 mo (range: 5–120 mo); follow-up started on the day of radical prostatectomy and concluded on 1 July 2005, or the date of

Table 9.1 The distribution of clinical and histopathological features as determined in the biopsy specimen of 281 participants who underwent radical prostatectomy. Spearman Rank Correlations for pairs of variables.

	N (% of total) †	Postoperative variables				
Preoperative variables	**Median (range) ‡**	**pT**	**RP Gleason score**	**Gleason grade 4/5, %**	**Surgical Margins, Yes/No**	**Tumor volume, mL**
Age, years						
	64 (55 – 73)	.114	.306 *	.177	.095	.125
Clinical tumor stage						
T1c	112 (39.9)	.194	.147	.174	.123	.192
T2a-c	165 (58.7)					
T3a	4 (1.4)					
Serum PSA (ng/mL)						
	5.2 (0.8 – 29.5)	.253 *	.112	.196	.141	.458 *
Number of positive for tumor biopsy cores						
1	101 (35.9)	.283 *	.182	.282 *	.249 *	.537 *
2	82 (29.2)					
3	49 (17.4)					
4-6	49 (17.4)					
Biopsy Gleason score						
2-6	203 (72.2)	.284 *	.443 *	.462 *	.095	.296 *
7	66 (23.5)					
8-10	12 (4.3)					
Length of tumor (mm)						
	7.2 (0.4 – 51.0)	.320 *	.273 *	.365 *	.298 *	.613 *
Length of high-grade cancer (mm)						
	0.0 (0.0 – 42.0)	.306 *	.450 *	.534 *	.09	.336 *
Proportion of high-grade cancer (%)						
	0.0 (0.0 – 100.0)	.290 *	.451 *	.528 *	.076	.300 *
Total	281					

PSA *Prostate-specific antigen*

RP *Radical Prostatectomy*

pT *Pathological Tumor Stage*

* *Correlation is statistically significant at the P <.001 level (2-tailed)*

† *N (%) for categorical variables*

‡ *Median (range) for continuous variables*

death. PSA relapse (≥0.1 ng/mL) occurred in 39 (13.9%) patients after a median follow-up of 21.0 mo (range: 1–97 mo). PSA relapse with subsequent rise of the PSA value above the 1.0 ng/mL threshold occurred in 24 (8.5%) cases, and 12 (50.0%) progressed clinically. Local disease progression and distant metastatic disease were found in 7 (2.5%) and 8 (2.8%) patients. All patients with clinical progression had PSA levels ≥1.0 ng/mL after treatment.

Preoperative features

In table 9.1 the distribution of preoperative variables is listed along with correlation with postoperative pathologic variables. For those with no high-grade cancer in the biopsy, 80.5% had ≤5% high-grade cancer in the prostate. For those with larger amounts (≥3 mm) of poorly differentiated components in the biopsy, 88.4% had substantial amounts (≥5%) of high-grade cancer in the prostate.

Cox proportional hazards models for PSA relapse and clinical recurrence of disease are shown in table 9.2 and table 9.3, respectively. Preoperative PSA level (p = 0.002), length of tumor (p = 0.040), and length of high-grade cancer (p = 0.006) in the biopsy were independent

Table 9.2 Cox Proportional Hazards Model for PSA-relapse after radical prostatectomy using clinical and histopathological variables as assessed in the biopsy specimen.

	PSA-Progression (≥0.1 ng/mL) after radical prostatectomy			
Preoperative	**Univariate analysis**		**Multivariate analysis**	
Variables	**HR**	***P*-Value**	**HR**	***P-Value***
Number of positive for tumor biopsy cores	1.439	.001		*ns*
Biopsy Gleason score				
2-6	Baseline †			
7	2.943	.001		*ns*
8-10	2.886	.045		*ns*
Length of tumor (mm)	1.055	<.001	1.012	*.04*
Length of high-grade cancer (mm)	1.079	<.001	1.033	*.006*
Clinical tumor stage				
T1c	Baseline ‡			
T2a-c	1.813	.095		*ns*
T3a	1.883	.532		*ns*
PSA-level (ng/mL)	1.117	<.001	1.120	*.002*

PSA *Prostate-specific antigen*

HR *Hazard ratio*

† *For biopsy Gleason score 7 and 8-10 combined, compared to baseline: HR= 3.617 (P< .001)*

‡ *For clinical tumor stage T2a-c and T3a combined, compared to baseline: HR= 1.950 (P = .069)*

ns *Not statistically significant*

Table 9.3 Cox Proportional Hazards Model for clinical progression of disease after radical prostatectomy using clinical and histopathological variables as assessed in the biopsy specimen.

	Clinical Progression after radical prostatectomy			
Preoperative	**Univariate analysis**		**Multivariate analysis**	
Variables	**HR**	***P*-Value**	**HR**	***P-Value***
Number of positive for tumor biopsy cores	1.513	.025		*ns*
Biopsy Gleason score				
2-6	Baseline †			
7	2.809	.076		*ns*
8-10	1.984	.512		*ns*
Length of tumor (mm)	1.037	.098		*ns*
Length of high-grade cancer (mm)	1.074	.004	1.074	*.004*
Clinical tumor stage				
T1c	Baseline ‡			
T2a-c	3.315	.122		*ns*
T3a	1.000	1.00		*ns*
PSA-level (ng/mL)	1.144	.021		*ns*

PSA *Prostate-specific antigen*

HR *Hazard ratio*

† *For biopsy Gleason score 7 and 8-10 combined, compared to baseline: HR= 3.177 (P= .050)*

‡ *For clinical tumor stage T2a-c and T3a combined, compared to baseline: HR= 3.043 (P = .151)*

ns *Not statistically significant*

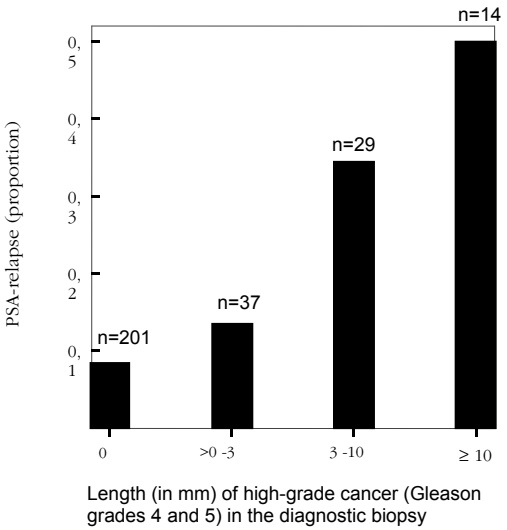

Figure 9.1 Bar representing the absolute length (mm) of high-grade cancer in the diagnostic biopsy and the proportion of men with PSA-relapse ≥0.1 ng/mL after radical prostatectomy

prognostic factors for PSA relapse ≥0.1 ng/mL. Length of high-grade cancer was the single independent prognostic factor for PSA relapse ≥1.0 ng/mL (p = 0.016) and clinical recurrence of disease (p = 0.004). Biopsy Gleason score was rejected in the final equations in the presence of high-grade components.

figure 1 shows PSA failure rates for 0, >0–3, ≥3–10 and ≥10 mm high-grade cancer in the biopsy. An increase of cumulative failure probability is shown with a rise of Gleason grades 4/5.

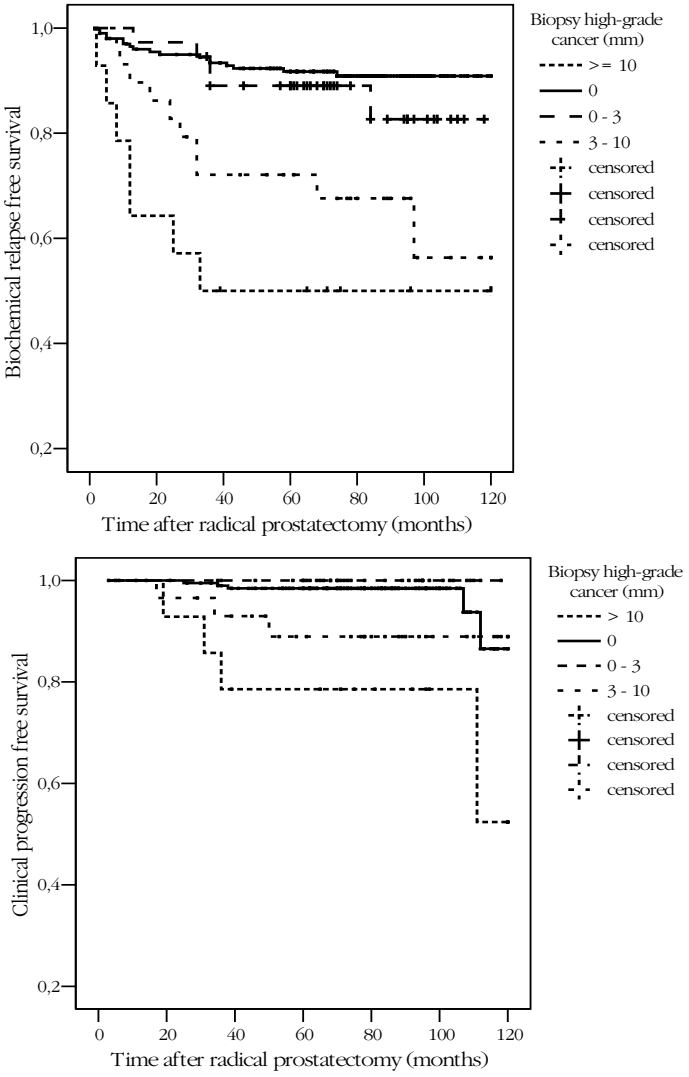

Figure 9.2 Kaplan-Meier curve of the probability of a.) biochemical (PSA ≥0.1 ng/mL) and b.) clinical disease recurrence (local relapse at the vesico-urethral anastomosis site, distant metastasis) after radical prostatectomy as a function of absolute length (in mm) of high-grade cancer in the diagnostic biopsy specimen

Table 9.4 The distribution of histopathological features as determined in the radical prostatectomy specimen of 281 participants who underwent radical prostatectomy. Association with PSA-relapse and clinical recurrence of disease after radical prostatectomy.

	Progression after radical prostatectomy		
	PSA (≥0.1 ng/mL)	PSA (≥1.0 ng/mL)	Clinical Progression
Postoperative Variables	N (% of total) † Median (range) ‡	N (% of total) † Median (range) ‡	N (% of total) † Median (range) ‡
Pathological stage*			
pT_2	18/211 (8.5)	9/211 (4.3)	3/211 (1.4)
pT_{3a}	10/49 (20.4)	4/49 (8.2)	1/49 (2.0)
pT_{3b-4}	11/21 (52.4)	11/21 (52.4)	8/21 (38.1)
RP Gleason score			
2-6	9/165 (5.5)	5/165 (3.0)	0/165 (0.0)
7	25/109 (22.9)	15/109 (13.8)	9/109 (8.3)
8-10	5/7 (71.4)	4/7 (57.1)	3/7 (42.9)
High-grade tumor involvement (%)	25 (0 – 100)	50 (0 – 100)	62.5 (25 – 100)
Surgical Margin Status			
Negative	17/215 (7.9)	10/215 (4.7)	8/215 (3.7)
Positive	22/66 (33.3)	14/66 (21.2)	4/66 (6.1)
Tumor Volume (mL)	1.32 (0.01 – 13.48)	1.42 (0.46 – 13.48)	1.63 (0.46 – 4.60)
Total	39/281 (13.9)	24/281 (8.5)	12/281 (4.3)

PSA *Prostate-specific antigen*

* *TNM 1997*

RP *Radical prostatectomy*

† *N (%) for dichotomized or categorical variables*

‡ *Median (range) for continuous variables*

The probability of biochemical and clinical relapse after radical prostatectomy as a function of length (in millimeters) of high-grade cancer is depicted in figure 9.2A and B, respectively.

Subsequently, we performed Cox multiple regression analysis with the same variables, but now with biopsy tumor involvement, and proportion (instead of absolute length in millimeters) of high-grade cancer. PSA level ($p = 0.032$), biopsy tumor involvement ($p = 0.002$), and proportion of high-grade cancer ($p = 0.001$) in the biopsy were independent predictors of PSA relapse ≥0.1 ng/mL.

When biopsy Gleason score 7 cancers were subcategorized into 3+4 and 4+3 cancers and analyzed further for prognostic significance, the amount of high-grade cancer (whether length or percentage) was the most important predictor of relapse, whereas the Gleason grading system was rejected in presence of high-grade components (figure 9.3).

Table 9.5 Cox Regression Analysis for PSA-relapse after radical prostatectomy using histopathological variables as assessed in the radical prostatectomy specimen.

Postoperative variables	PSA-Progression (≥0.1 ng/mL) after radical prostatectomy			
	Univariate analysis		Multivariate analysis	
	HR	*P*-Value	HR	*P-Value*
Extraprostatic extension (pT3a)*	1.529	.249		*ns*
Invasion of adjacent organs (pT3b – pT4)*	6.852	< .001	2.766	*.013*
RP Gleason score				
2-6	Baseline			
7	2.942	.001		*ns*
8-10	9.937	< .001		*ns*
High-grade tumor involvement (%)	1.029	< .001	1.023	*<.001*
Positive surgical margins	4.619	<. 001	3.169	*.001*
Tumor Volume (mL)	1.401	<. 001		*ns*

PSA *Prostate-specific antigen*
RP *Radical prostatectomy*
HR *Hazard ratio*
* *TNM 1997*
ns *not statistically significant*

Postoperative features

table 9.4 and table 9.5 show that only the proportion of high-grade cancer ($p < 0.001$), pT3b-pT4 ($p = 0.013$) and surgical margin status ($p = 0.001$) remained in the equation models after multiple Cox regression analysis. Gleason score was rejected in the presence of high-grade components. For PSA ≥1.0 ng/mL as a criterion of PSA relapse, and clinical relapse, pT3b-pT4 ($p < 0.001$, both analyses) and percentage of high-grade cancer ($p = 0.002$ and $p = 0.005$, respectively) were independent prognosticators.

DISCUSSION

Radical prostatectomy has become a common procedure in patients diagnosed with early prostate cancer, and the intervention is reported to reduce disease-specific mortality, overall mortality, and the risks of metastasis and local progression.[113] Whether the surgical procedure itself is of benefit for individual patients depends on a constellation of variables such as patient age, serum PSA level, tumor extent, histologic grade of disease, and the remaining life

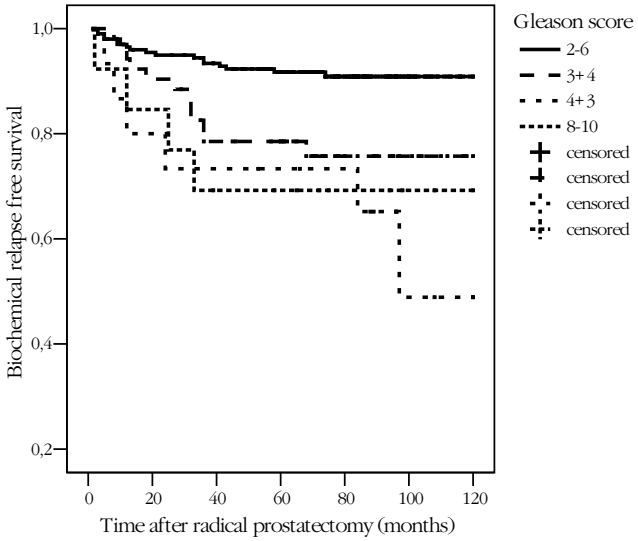

Figure 9.3 Kaplan-Meier curve of the probability of biochemical (PSA ≥0.1 ng/mL) relapse after radical prostatectomy as a function of biopsy Gleason score (2-6, 3+4, 4+3, 8-10)

expectancy of the patient diagnosed with cancer. In prostate cancer screening programs, no reliable set of prognostic parameters exists today that accurately distinguishes patients with nonaggressive disease from those with fatal disease beyond cure. Such tools are required because it is considered that a substantial proportion of screen-detected prostate cancers have been overdiagnosed, whereas others might not have been detected (and treated) early enough.[37] In the counseling of patients who are to benefit from radical treatment, or who have a substantial risk of (early) disease recurrence after definite treatment, a careful individual risk assessment at the time of diagnosis is mandatory.

In the PSA era, established prognostic factors as clinical tumor stage, biopsy Gleason score, and PSA level are losing clinical utility because the vast majority of cases with newly detected prostate cancer have clinically localized disease and have cancers of intermediate grade, that is, biopsy Gleason scores 6 and 7.[164] Low-grade tumors (Gleason scores 2–5), and high-grade tumors (Gleason scores 8–10) become a relatively rare finding. It was further reported that on repeated screening, even the serum PSA test loses its predictive power for both the detection of prostate cancer and the identification of adverse prognostic tumor features and patient outcome.[165,166] Therefore, more sensitive tools for stratification of patients into prognostic risk groups are needed. For now, no molecular markers exist that give validated prognostic information superior to conventional histopathologic features, so more scrutiny on the prognostic value of well-established histopathologic variables is warranted. Prior studies have attempted to establish whether the subclassification of Gleason score 7 cancers (3+4 versus 4+3) as determined in the radical prostatectomy specimen provides further information

about patient outcome.[167-174] Besides the finding that the rates of disease-free survival after radical prostatectomy for patients with Gleason scores 7 appear to be intermediate between patients with Gleason score ≤6 and ≥8, the distinct and heterogeneous behavior of tumors within the Gleason score 7 group itself is striking.[167] This can, in part, be explained by the observation that a single Gleason score 7 varies in its percentage of Gleason grades 4/5 from 5% to 95% without altering the total score. Even small amounts of high-grade cancer in the radical prostatectomy may, according to some authors, alter the biologic aggressiveness of disease as reflected by an increased biochemical recurrence rate after radical prostatectomy compared to those without high-grade components.[173] Therefore, it seems plausible that a categorization of tumors according to their amount of high-grade cancer is prognostically more important than a sub-classification of Gleason score 7 cancers into just two categories. A few studies confirmed this view by showing independent prognostic value for the proportion of Gleason growth patterns 4/5 in the radical prostatectomy specimen for biochemical recurrence.[155,156,174]

For the pathologist this may sometimes be difficult to perform because pattern 4 seems to evolve from pattern 3. On the other hand, Gleason grading is microscopically a low-power exercise, and criteria for grade 4/5 are well-established.[157] Furthermore, according to most authors a very limited amount (<5%) of high-grade cancer in the radical prostatectomy specimen does not seem to have a major impact on prognosis (own data).[155,156] The same seems to hold true for the presence of a minor amount of high-grade cancer in needle biopsies (our data, not shown). This should allow a relatively consistent estimation of the percentage of high-grade cancer in both needle biopsies and prostatectomy specimens.

Following radical prostatectomy, the proportion of high-grade cancer was an independent predictor of outcome for PSA ≥0.1 ng/mL, PSA ≥1.0 ng/mL as a criterion of PSA relapse, and clinical progression of disease. Our data indicate that the percentage of high-grade cancer in the radical prostatectomy was superior to the original Gleason score in predicting outcome of patients who underwent radical prostatectomy. These findings are in line with those of others.[155,156,174]

Our data further indicate that the amount of Gleason growth patterns 4/5 in the diagnostic biopsy (whether absolute length or proportion) is an important predictor of adverse prognostic factors in the radical prostatectomy specimen (table 9.1). In absence of high-grade cancer in the biopsy, >80% had minor (≤5%) amounts of high-grade cancer in the prostatectomy specimen. In those with larger amounts (≥3 mm) of poorly differentiated components in the biopsy, almost 90% had substantial and prognostically important amounts of high-grade cancer in the surgically treated prostate. Thus, a good correlation was found between the amount of high-grade cancer in the biopsy and that within the corresponding radical prostatectomy

specimen. The amount of high-grade cancer in the biopsy proved to be an independent and stronger prognostic factor for outcome (PSA ≥0.1 ng/mL, PSA ≥1.0 ng/mL, clinical relapse) after radical prostatectomy than Gleason score.

Several caveats may limit the interpretation of our data. First, it should be acknowledged that PSA relapse after radical local treatment is a questionable surrogate and a not proven end point for clinical relapse and disease-specific mortality. Only a fraction of asymptomatic men with PSA relapse will experience local or distant disease progression or death from prostate cancer. Pound et al., who reported on a relatively adverse prognostic cohort as reflected by a 45.6% organ-confinement rate after radical prostatectomy, showed that the 3-, 5-, and 7-yr metastasis-free rates after radical prostatectomy with subsequent PSA relapse were 78%, 63%, and 52%, respectively, without additional therapeutic intervention.[88] Caution should be kept in generalizing our results because the number of men reaching a clinically relevant end point is limited.

Second, the follow-up period may still be too short for those with PSA relapse to progress clinically. Johansson et al. reported that in a cohort of initially untreated men with localized prostate cancer, tumor progression developed even after 15 yr of follow-up.[109] Pound et al. reported that the median time to metastatic progression in those with a rising PSA level after radical prostatectomy was 8 yr, longer than our median follow-up of 7 yr.[88] The number of cases progressing clinically might thus further increase with continued follow-up. On the other hand, it is likely that the majority of cases with PSA relapse have already been identified in our study, because it is recognized that >80%–90% of patients undergoing radical prostatectomy will have a relapse within 5 yr after surgery.[88,175]

Third, patient selection and participation bias may be introduced in our study due to the observation that all men included were candidates for radical prostatectomy. These men are younger, healthier, and have longer life expectancy compared to those who underwent external-beam radiotherapy. The figures reported herein do only apply for those who eventually consider radical prostatectomy, the preferred treatment modality for prostate cancer.

And fourth, arbitrary cut-off levels for the amount of high-grade cancer in the biopsy were used in our analyses. There are no generally accepted breakpoints for grouping subjects according to the amount of high-grade cancer in the biopsy, as there are for Gleason score and PSA level. Also, there are no recommendations to use either the absolute or relative amount of high-grade cancer in the biopsies. An attempt was made to obtain clinically practical definitions.

CONCLUSIONS

In the present study, the amount of high-grade cancer in the diagnostic biopsy proved to be an independent and stronger prognostic factor for relapse (PSA ≥0.1 ng/mL, PSA ≥1.0 ng/mL, clinical relapse) after radical prostatectomy than Gleason score. Therefore, we propose that, in addition to the Gleason score, the amount of Gleason growth patterns 4/5 in the biopsy (whether absolute length or proportion) should be mentioned in the pathology report.

Chapter 10

Nomogram use for the prediction of indolent prostate cancer: impact on screen-detected populations

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Cancer; in press

ABSTRACT

Background

Screening for prostate cancer has resulted in an increased incidence-to-mortality ratio. Not all cancers deserve immediate treatment. It has therefore become more important to be able to identify those cases of screen-detected prostate cancer most likely to show indolent behavior.

Patients & Methods

The Kattan-nomogram for the prediction of indolent prostate cancer has been validated and re-calibrated for use in a screening setting. The recalibrated nomogram was used to calculate the number of men who were predicted to have indolent cancer in a screen-detected cohort from the European Randomized study of Screening for Prostate Cancer (ERSPC), section Rotterdam.

Results

Of 1,629 cancers detected in two subsequent screening rounds 825 were suitable for nomogram use. The remainder was very unlikely to have indolent cancer. A total of 485 men (485 / 825=59%) were predicted to have indolent cancer, which is 30% (485 / 1,629) of all screen-detected cases. Cancers found at repeated screening after four years had a higher probability of indolent cancer than cases from the prevalence screening (44% vs. 23%; P<.001).

Conclusion

The current nomogram can identify substantial groups of screen-detected cancers which are likely indolent and can therefore be considered for active surveillance.

INTRODUCTION

Screening diagnoses prostate cancers earlier in their natural course. Moreover, screening leads to the detection of prostate cancers that would not have surfaced clinically in the absence of screening (i.e. overdiagnosis).[37] This has resulted in an increased incidence.[33] However, a considerable proportion of the detected cancers will not lead to death. In order to counsel between immediate treatment and active surveillance with the possibility for deferred curative treatment, it is important to risk-stratify patients at the time of diagnosis. Recently, different nomograms for the risk assessment of prostate cancer have been described.[12,176-178] The nomogram of Kattan et al. predicts the probability of indolent prostate cancer in a clinical setting.[12] It has been validated and re-calibrated for use in a screening setting by Steyerberg et al in a subgroup of men diagnosed with prostate cancer in the ERSPC.[108] We applied the latter nomogram to men diagnosed in the screening program of the European Randomized study of Screening for Prostate Cancer (ERSPC) section Rotterdam in order to estimate the proportion of indolent cancers.[101]

PATIENTS & METHODS

The Rotterdam section of the ERSPC has randomized 42,376 men and a PSA-based screening program with a four-year interval was offered to men allocated to the screening arm (figure 10.1).[101] Lateralized sextant systematic biopsies were obtained. The nomogram was applied to men identified with screen-detected prostate cancer comprising the following features: 1) clinical stage T1c or T2 disease, 2) PSA 20 ng/mL or less, 3) primary and secondary Gleason grade 3 or less, 4) positive cores 50% or less, 5) total cancer in biopsy cores 20 mm or less and 6) benign tissue in all cores 40 mm or more. The range of predictor variables of detected cancers appear in table 10.1. Men who do not match the stated criteria are very likely to have more advanced cancers, which are therefore very unlikely to be indolent. Indolent cancer was defined by a total tumor volume less than 0.5 cc, confined to the prostate (no focal or established extra-capsular extension) and with no Gleason pattern 4 or 5.[179,180] The number of men with indolent disease was estimated by the sum of the probabilities for indolent cancer (i.e. cumulative probability). The exact formula to calculate the probability of indolent cancer is given under table 10.2

RESULTS

Of 1,629 cancers detected in two subsequent screening rounds 825 (51%) were suitable for nomogram use according to the given criteria. A total of 485 of the 825 men suitable for

Table 10.1 Predictive variables of all men detected with prostate cancer in the prevalence screening (i.e. round 1) and the repeat screening after four years (i.e. round 2) in ERSPC Rotterdam

		Screen round 1	Screen round 2	Total	P-value
Prostate cancer	**Number**	**1,079**	**550**	**1,629**	
PSA (ng/mL)	**Median (25-75p)**	5.7 (3.9-9.3)	3.9 (3.1-5.4)	**4.8 (3.5-7.7)**	*<.001**
	<= 20 ng/mL (%)	992 (92)	541 (98)	**1533 (94)**	*<.001***
Prostate vol. (cc)	**Median (25-75p)**	37.2 (29.3-49.1)	38.2 (30.1-49.6)	**37.6 (29.5-49.3)**	*.34**
Clinical stage	**T1c (%)**	398 (37)	344 (63)	**742 (46)**	*<.001***
	T2 (%)	534 (50)	198 (36)	**732 (45)**	
Biopsy Gleason grade	**Primary <=3 (%)**	988 (92)	521 (95)	**1,509 (93)**	*.02***
	Secondary <=3 (%)	711 (66)	449 (82)	**1,160 (71)**	*<.001***
% Pos cores	**Median (25-75p)**	40.0 (22.5-57.1)	33.3 (16.7-50.0)	**33.3 (16.7-50.0)**	*<.001**
	<= 50% (%)	752 (70)	476 (87)	**1228 (75)**	*<.001***
Mm PC	**Median (25-75p)**	7.6 (3.3-18.4)	3.4 (1.4-7.9)	**5.8 (2.5-14.4)**	*<.001**
	<= 20 mm (%)	835 (77)	511 (93)	**1346 (83)**	*<.001***
Mm non PC	**Median (25-75p)**	55.8 (44.8-66.0)	68.4 (61.2-75.2)	**60.8 (49.2-70.3)**	*<.001**
	>= 40 mm (%)	900 (83)	531 (97)	**1431 (88)**	*<.001***

*	*Mann-Whitney U test*
**	*Chi square test*
PC	*Prostate cancer*
25-75p	*25th and 75th percentile*
PSA	*Prostate-specific antigen*
Prostate vol. (cc)	*The prostate volume was determined using 5mm-step-section planimetry*
% Pos cores	*Proportion of biopsy cores involved with prostate cancer*
mm PC	*Total millimetres of cancer tissue in all biopsy cores*
mm non PC	*Total millimetres of benign tissue in all biopsy cores*

application of the nomogram (485 / 825 = 59%) were predicted to have indolent disease. If one assumes that none of the cases excluded for nomogram use were indolent (N=804), an estimated 30% (485 / 1,629) of all screen-detected men were predicted to have indolent disease. In the prevalence screen 455 men (42%; 455 / 1,078) were eligible for nomogram use and an estimated 243 (53%; 243 / 455) were predicted indolent, which is 23% of 1,078 cancers detected in the first screening round. In the repeat-screen after four years, 550 cancers were detected, 370 (67%; 370 / 550) were eligible for nomogram use and 242 (65%; 242/370) were classified as predicted indolent; 44% of all 550 cancers detected by repeated screening.

Many men eligible for nomogram use underwent radical prostatectomy (N=336; 41%), including the 278 used for the re-calibration of the Kattan nomogram. The remainder elected radiation therapy (N=274; 33%), watchful waiting (207; 25%) or hormonal treatment (N=4; 1%); the initial treatment modality was unknown in 4 men (1%).

Although the number of indolent cancers can be estimated by taking the sum of the probabilities for indolent cancer (i.e. the cumulative probability), it is at present impossible to individually identify these patients. Therefore, a cut-off point for the probability of indolent

Table 10.2 Cumulative probabilities of predicted indolent prostate cancer of men detected with prostate cancer in the prevalence screen (i.e. round 1) and the repeat screen after four years (i.e. round 2)

		Screen round 1 **Number (%)**	**Screen round 2** **Number (%)**	***Total*** **Number (%)**
Prostate cancer		**1,079**	**550**	**1,629**
Indolent**		243 (23) *	242 (44) *	**485 (30)**
Probability for indolent prostate cancer	**> 30%**	380 (35) *	350 (64) *	**730 (45)**
	> 40%	316 (29) *	320 (58) *	**636 (39)**
	> 50%	256 (24) *	294 (54) *	**550 (34)**
	> 60%	185 (17) *	247 (45) *	**432 (27)**
	> 70%	124 (12) *	181 (33) *	**305 (19)**
	> 80%	65 (6) *	92 (17) *	**157 (10)**
	> 90%	16 (2)	12 (2)	**28 (2)**

Numbers are the sum of the predicted probabilities of indolent cancer as calculated with the recalibrated Kattan nomogram.

The exact formula to calculate the probability of indolent cancer is:

*P(indolent) = 1 / (1+exp(-[-4.196 + 0.25 * score])], where score = -5*(ln(PSA)-3) [in ng/ml] + 0.1*(US volume-20) [in cc] + 4*Gleason22 [0 if false, 1 if true] + 1*Gleason23 [0 if false, 1 if true] -3*(ln(mm cancerous tissue)-3) + 0.1*(mm non-cancerous tissue-40)*

* *Mann-Whitney Test: P-value <.001 for difference in P(ind) between round 1 and 2.*

** *Calculated in 455 (round 1), 370 (round 2) and 825 (total) men suitable for nomogram use.*

cancer is required for clinical decision making on further therapy. This cut-off value depends on the level of acceptable primary undertreatment of potentially aggressive cases resulting from delay of active treatment in those men who are misclassified. Table 10.2 shows numbers of men with increasing cut-off points for the probability of indolent prostate cancer (>30% to >90%). We note that 27% (N=432) of all cancers and 45% (N=247) of cancers diagnosed in round two would be classified as indolent with a cut-off of 60%. Using that cut-off, 31% of the current cohort chose for watchful waiting and 33% for radical prostatectomy.

DISCUSSION

Overdiagnosis (and overtreatment) are defined as the diagnosis (and treatment) of cancers which would never surface during the lifetime of their carrier (and would therefore be treated unnecessarily). Obviously, both parameters are co-determined by disease related factors and by the natural life expectancy of a given patient. A tumor classified as non-indolent whose carrier dies of intercurrent disease was also overdiagnosed.[37] Men with indolent disease are often subjected to overtreatment due to the difficulty and uncertainty of being able to predict the presence of indolent prostate cancer. These men are unnecessarily subjected to the burden of treatment and to potential complications with no impact on the survival of the disease. With more solid information active surveillance strategies can be advised more strongly, making use of reasonable cut-offs for the probability of indolent prostate cancer.

Evidence accumulates that wrongly selected men and men with dedifferentiating tumors will surface through active surveillance using PSA kinetics and repeated biopsies.[181-185]

We assumed that no indolent prostate cancers were present in men not suitable for nomogram use. Although this has led to an underestimation, it is highly unlikely that men who do not match the eligibility criteria have indolent cancer (i.e. those with clinical stage T3 or higher disease, PSA over 20 ng/mL, primary and secondary Gleason grade 4 or higher, positive cores over 50%, total cancer in biopsy cores over 20 mm, or benign tissue in all cores less than 40 mm). Nevertheless, if the underestimated 30% of predicted indolent cancers in the first two screen rounds of the ERSPC would be extrapolated to a heavily screened population such as the U.S., where 234,460 men are annually diagnosed with prostate cancer 69,869 would have predicted indolent disease.[33] Those men could avoid immediate treatment and may avoid treatment at all.

Although the absence of poor prognostic factors suggests that these tumors are unlikely to influence longevity,[110] the application of active surveillance for predicted indolent cases has not conclusively been shown to be safe in avoiding disease progression and prostate cancer death while on observation.[186] It is therefore not definitively known whether these really are the cancers which can be left untreated and observed. Moreover, tumors which have a high probability to be indolent could appear to be important prostate cancers due to biopsy undersampling and dedifferentiation.[187] However, given the minimal improvement in cancer-specific survival when comparing surgical treatment to no treatment among men with cancers not detected by screening,[113] it seems unlikely that active surveillance of low-risk, screen-detected cancers will place patients at an undue risk of an adverse outcome.

Clinical validation of the endpoint 'indolent prostate cancer probability' with use of outcome data of untreated men is mandatory. Furthermore, the present nomogram requires further validation and updating for use in men excluded in the previous analyses and for men diagnosed by more extensive biopsy sampling.[12]

With the screening regimen used in this study (ERSPC Rotterdam) the proportion of overdiagnosed cases is estimated to be 54% of all diagnosed cancers.[37] It is unknown which proportion is classified as overdiagnosed because of intercurrent mortality. On this background, the suggested capability of diagnosing indolent disease in 30% of all screen-detected cases seems to be an important step.

CONCLUSION

The current nomogram for screen-detected prostate cancer can assist in identifying substantial groups of prostate cancers which are likely indolent and can be considered for active surveillance.

PART IV

ACTIVE SURVEILLANCE AS A WAY OUT OF THE OVERDIAGNOSIS DILEMMA

Chapter 11
Management and survival of screen-detected prostate cancer patients who might have been suitable for active surveillance
Eur Urol. 2006 Sep;50(3):475-82

Chapter 12
Active surveillance for prostate cancers detected in three subsequent screening rounds: characteristics, PSA kinetics and outcome
Eur Urol. 2007 May;51(5):1244-50

Chapter 11

Management and survival of screen detected prostate cancer patients who might have been suitable for active surveillance

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ABSTRACT

Background

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. It is for ethical, medical and economical reasons important to define which patients can be managed by active surveillance.

Patients & 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 PSA, digital rectal examination and transrectal ultrasound. For this study, men with criteria that reflect current active surveillance studies were selected: men with a biopsy Gleason score <=3+3 in 2 cores or less, with a PSA density lower than 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%) matched the criteria for active surveillance. Their mean age was 65.7 years 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 8-year prostate cancer-specific survival was 99.2%, while the overall survival was 85.4%. Nineteen men on watchful waiting changed to definitive treatment during follow-up.

Conclusion

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

INTRODUCTION

Screening has caused a marked increase in prostate cancer incidence, while it is unclear whether the stage and grade shift which has been caused by prostate-specific antigen (PSA)-based screening reduces the prostate cancer mortality.[188] For the US, it is estimated that more than 230,000 men will be diagnosed with, and 30,000 will die of prostate cancer in 2005. 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.[27] Most of the cancers diagnosed at low PSA-values have good risk, low-grade tumors, which would not have been diagnosed in the absence of screening (i.e. overdiagnosis).[189] 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.[145,190] Therefore, the present challenge should be to identify those cancers which need treatment and which 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. By means of the PSA-kinetics, digital rectal examinations (DRE) and repeat biopsies, this goal should be achievable. Expectancy is maintained until the patient dies of other causes, until he receives definitive treatment or until he 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, the DRE and the pathological features of the biopsy.[191] 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 matched criteria typically designed for an active surveillance program.

PATIENTS & 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.[78] 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 start until May 1997 men were offered a lateral sextant biopsy if either the PSA level was ≥4.0 ng/mL, the DRE and/or the TRUS was suspect 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, CA), which was replaced after January 2000 by the automated version (Beckman-Access; Beckman-Coulter Inc., Fullerton CA).

Definition

Watchful waiting entails a strategy for all men who are managed expectantly, whereas active surveillance focuses on those men in whom therapy is delayed until the tumor 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 SPG4 trial.[113]

Study population

The criteria we considered acceptable for enrolment in an active surveillance protocol were: (1) a biopsy Gleason score <=3+3, (2) a maximum of two cores invaded with prostate cancer, (3) clinical stage T1C or T2, (4) a PSA-density (PSA D) smaller than 0.2 ng/mL/cc and (5) a PSA-level below 15 ng/mL. The criteria we considered appropriate for active surveillance strategies were defined according to the literature; furthermore are they based on analysis of the data ERSPC has generated so far.[110,191,192] Those men who were diagnosed in the prevalence screen of the ERSPC and who fulfilled the criteria were selected as our study population.

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 anonymized patient charts.[148] The review of men diagnosed in the first round of screening was complete until January 1st 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.[80] 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.

Follow-up

Patients were seen at 3-month intervals within 1 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.[193] The median follow-up was 79.4 months (mean 80.8; range 6.8-129.8) and was equal in the treatment arms.

Pathologic processing

Systematic, lateralized sextant biopsies were obtained during longitudinal and cross-sectional ultrasonographic scanning of the prostate.[83] A seventh, lesion directed biopsy was taken in case of a hypo-echogenic lesion. Prostate biopsy cores were labeled and processed individually. One pathologist (TvdK) 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 of the Rotterdam region. There was a single protocol for total embedding of the prostate in use in all pathology laboratories, allowing accurate measurements of tumor volume, grading, and staging.[194] In short, after fixation, radical prostatectomy specimens were inked and serially sectioned at 4-mm intervals, and they were embedded totally in paraffin blocks. After a pathology review, pathologic disease stage, and Gleason score were determined.[84] Tumor volume was measured by morphometry, as described previously.[195] For tumor staging of radical prostatectomy specimens, the 1992 TNM classification system for prostate carcinoma was used.[196]

Statistics

For statistical analysis the commercially available software SPSS was used (version 12.0.1; SPSS, Inc., Chicago, IL). 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.

RESULTS

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 19,970 men were actually 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 years (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 men (21.9%) were managed by watchful waiting. One man received hormonal treatment and in another patient no treatment was initiated, because he deceased very shortly after the prostate cancer diagnosis. The baseline characteristics are shown in table 11.1.

Radical prostatectomy

Table 11.2 shows that the median volume of tumors found in 117 radical prostatectomy specimens was 0.24 mL. (mean 0.49; range 0.001-4.71); in 34 prostates (29.1%) the tumor volume was more than 0.50 mL. In five prostates (3.9%) capsular perforation was present, vascular infiltration was present in 2 and seminal vesicle infiltration in 1 prostate. Undersampling in Gleason score (i.e. undergrading) was present in 23 men (17.6%), of whom two (1.5%) had a Gleason score of the radical prostatectomy specimen higher than 7 (5+4=9 and 5+3=8).

Radiotherapy

Radiotherapy was elected by 91 men: external beam radiotherapy by 88 and brachytherapy by 3. 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 out of the three men, the other two received additional external beam radiotherapy, with dosages 45 and 68 Gray.

Table 11.1 Characteristics at baseline for all 293 patients with tumors which met the criteria for active surveillance

		RP	RT	WW	*Total*	*P-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%)	*0.020** (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 11.2 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

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 2 men; both had organ-confined disease. Radiotherapy was provided in 13 men; two of them 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 2 Gray). Four men received hormonal treatment. The major reason for deferred treatment was an increasing PSA-level.

Outcome

During a mean follow-up of 80.8 months, three men died from prostate cancer (1 radical prostatectomy, 2 radiotherapy) and 40 men died from intercurrent disease (table 3). After 8-years, the prostate cancer-specific survival was 99.2% and the overall-survival was 85.4% (figure 11.1). The baseline characteristics of men who died from prostate cancer or developed metastases are stated in table 4.

Metastatic disease developed in 2 men who elected radical prostatectomy and in 2 radiotherapy patients; three of those died as a result of prostate cancer. The fourth man was still at risk at December 1st 2005. His last PSA-level was 555 ng/mL, but he was active and feeling well.

Table 11.3 Outcome for all 293 patients with tumors which 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 11.4 Characteristics of men who developed metastatic disease

		Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
	Treatment	RP	RP	RT	RT
Characteristics At baseline	*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*

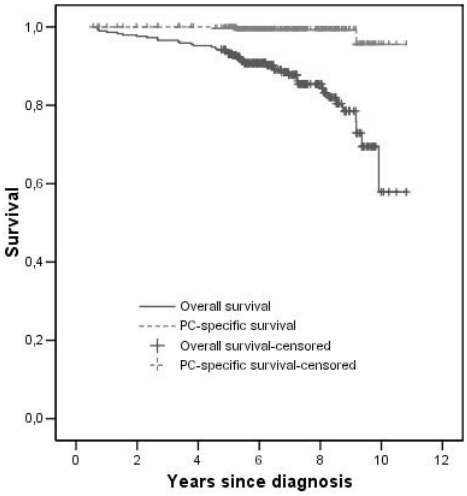

Figure 11.1 Kaplan-Meier graph of the overall and disease specific mortality.

PC-specific survival

Overall survival

Men at risk

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

Biochemical progression was present in 13 radical prostatectomy patients (9.6%) and 16 radiotherapy patients (17.6%). The 8-year biochemical 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-value=0.12).

With a mean 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, 8 men (17.8%) died of other causes.

DISCUSSION

This study describes the treatment and follow-up of screen detected prostate cancer patients with baseline characteristics currently regarded suitable for active surveillance. Men were treated by radical prostatectomy, radiotherapy or watchful waiting. The high disease specific survival (99.2% after 8 years) is in sharp contrast with the overall survival of 85.4%. The results of all treatment modalities applied to candidates for active surveillance in this study also

contrasts with the five year biochemical progression-free survival rates of 75.0% in radical prostatectomy patients, 77.5% for radiotherapy patients and 58.3% for patients with hormonal treatment.[189] The follow-up of the watchful waiters showed that the natural course of these selected cancers is favorable. In addition, the radical prostatectomy specimens showed disease characteristics of men who matched the active surveillance criteria as well. Although the prognostic factors of the radical prostatectomy group were significantly less favorable 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 favorable 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 4 years. Re-screening has been described to result in an ongoing downstaging of tumours.[197] Therefore, the proportion of men who are suitable for active surveillance will only increase when men have had a PSA recording earlier in their life. 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). It is evident that 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 which used the ERSPC Rotterdam data.[37] They came to an overdiagnosis rate of 27%-56% for men who were screened once and were in the age range of 55 to 75. Until new biomarkers become available, PSA will be used as a screen test; the future results of screening studies in Europe and the US are destined to influence the intensity of PSA-testing more than the question whether the test should be used for screening purposes at all.[18] The current challenge lies therefore in selecting those cancers which do not need treatment, or at least not at the time they are diagnosed. Thereby, the overtreatment as a result of overdiagnosis is minimized and the treatment related toxicity can be avoided.[145,190]

The objective of active surveillance policies should be to include those men in whom it seems safe to defer treatment; during the period of surveillance those 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 during their lifetimes. In our cohort 14.1% of men initially managed on a watchful waiting policy have already died as a result of other causes, while no metastatic disease developed. The prostate cancer-to-intercurrent death ratio in this study was 3/41=7.0%, meaning that for every man who dies of prostate cancer, more than 13 men decease with prostate cancer, but from other causes. The overall life expectancy for Dutch men aged 65.5 is 15.4 years, thereby reaching an age of 80.9 years.[198] The mean age for men from our study group who were alive

at January 1st 2005 was 72.3 years (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 5 years.[88] 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 in recognition of 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 biological 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.[102] The third pillar of patient selection is in the pathological features of the biopsy specimen. Currently, more research is invested in adequate sampling of the prostate. The value of a uniform application of sextant biopsies in all prostates has been debated.[199] In order 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 biopsies should be individualized.[200] Unfortunately, few studies exist which investigated the prognostic value of the tumor volume on the outcome.[201] The undersampling rate is likely to increase with increasing prostatic size, although one study reported the opposite.[202] The radical prostatectomy specimens of men who matched our active surveillance criteria on beforehand illustrate the undersampling of prostates in our study: 6.1% of men were shown to have a pathological stage that was higher than the expected pT2, and 17.5% had a Gleason score of more 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 in order to allow a proper estimation of the tumor volume and the 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.[203] Extensive sampling of the prostate has been shown to estimate tumor volume with reasonable precision.[187] 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.

CONCLUSION

Among those men fulfilling 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 initially managed with watchful waiting have died as a result of other

causes; contrasted 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, undersampling 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.

Chapter 12

Active surveillance for prostate cancers detected in three subsequent screening rounds: characteristics, PSA kinetics and outcome

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ABSTRACT

Objective

To study active surveillance as a management option for the important number of prostate cancer patients that would not have been diagnosed in the absence of screening.

Patients & 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 dependent 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 years (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 years, a total of 103 men (44.2%) had a PSA doubling time which was negative (i.e. half-life) or longer than 10 years. Men detected at re-screening 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 89.0% after eight years; the cause-specific survival was 100.0%.

Conclusion

This report shows a beneficial outcome, although preliminary, 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. It furthermore 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.

INTRODUCTION

Prostate cancer is an important cause of death in males. It is after lung cancer the second most important cause of cancer-related death in American males.[33] With the introduction of prostate-specific antigen (PSA) in the late 1980s a screening tool became available which has proved to detect prostate cancers earlier in the course of the disease.[24] One of the downsides of screening is a frequent diagnosis of low-risk cancers which would not have been detected during the man's lifetime in the absence of screening (i.e. overdiagnosis). As screening becomes globally more prevalent, the side-effects such as overdiagnosis will increase as well. It can be calculated that if all U.S. men with PSA levels ≥ 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.[30] 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.[204]

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.[28] Although several studies have examined the role of watchful waiting prior to the widespread use of PSA,[109,110,205] the natural course of screen-detected prostate cancer is less well known.[206,207] Screen-detected prostate cancer is different 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 Sprostate cancerG-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 four years.[61] 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 is an acceptable number of patients that need to be treated to prevent one prostate cancer death.[208] 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.[145,146]

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.

PATIENTS & 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.[78] 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 four-year interval. From start until May 1997 men were offered a lateral sextant biopsy if either the PSA level was ≥ 4.0 ng/mL, the digital rectal examination (DRE) and/or the transrectal ultrasound (TRUS) was suspect for carcinoma. From 1997, only a PSA ≥ 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 hypo-echogenic lesion.

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 15 ng/mL or less
3. Biopsy Gleason score less than 8

The cut-off date for this analysis was January 1st 2006. By then, the first and second round of the Rotterdam section of the ERSPC were completed; the third round will be finished in December 2007. The choice of initiating and continuation of 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.

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 anonymized patient charts.[148] 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.

Follow-up

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

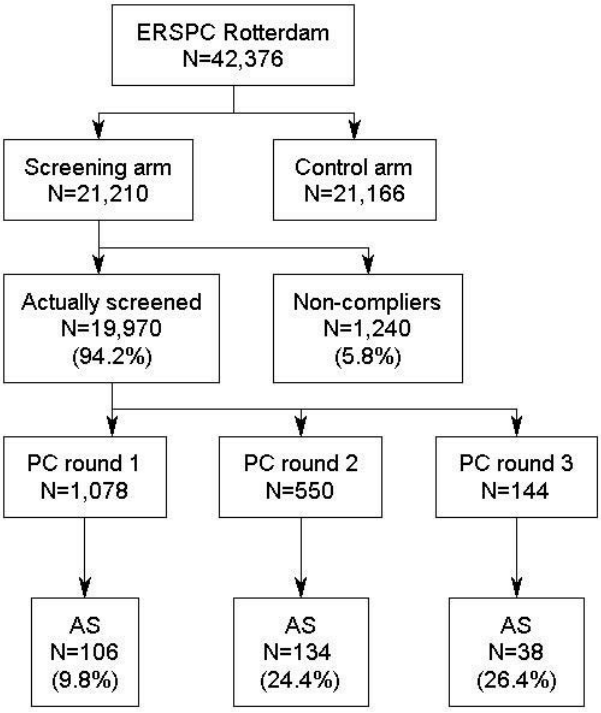

Figure 12.1 CONSORT-diagram of men screened for prostate cancer in the first three screening rounds of the Dutch branch of the ERSPC

PC Prostate cancer

AS Active surveillance

Statistics

To calculate PSA doubling time (PSADT) the base 2 logarithm of the PSA value was calculated using 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 only calculated in patients with 3 or more PSA values acquired prior to a possible therapy change. For statistical analysis the commercially available software SPSS was used (version 12.0.1; SPSS, Inc., Chicago, IL). 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.

RESULTS

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 screen round 1,078 men were diagnosed with prostate cancer (figure 12.1). Of those, 106 men (9.8%) elected active surveillance. In the second screen round 550 prostate cancers were detected and 134 (24.4%) of those elected active surveillance. In the incomplete third round 144 prostate cancers were diagnosed and 38 (26.4%) elected active surveillance. Of the 1,772 cancers detected in the first, second and third round 278 men (15.7%) elected active surveillance. At diagnosis, the study population had a median age of 69.8 years 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 are shown in table 12.1 were not significantly different. The median follow-up time was 3.4 years; 6.0 years for round 1 men, 3.2 years for round 2 and 1.2 years for those detected in round 3.

Table 12.1 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 (years)	***Median***	69.4	69.9	70.5	**69.8**	*0.45***
	(25-75p)	(65.7-72.4)	(65.9-73.1)	(67.3-73.3)	**(66.1-72.8)**	
PSA (ng/mL)	***Median***	4.2	3.4	3.8	**3.6**	
	(25-75p)	(3.3-5.5)	(2.6-4.4)	(3.3-5.6)	**(3.1-4.8)**	
	0-5	72 (67.9)	119 (88.8)	27 (71.1)	**218 (78.4)**	*<0.001**
	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)	**17 (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)**	

* *Chi-square test*

** *Kruskal Wallis test*

*** *Round 3 will be complete in December 2007*

PC *Prostate cancer*

AS *Active surveillance*

25-75p *25th and 75th percentile*

Deferred treatment

Of 278 men initially managed on an active surveillance policy, 82 (29.0%) received deferred treatment after a median of 2.5 years (25-75p; 1.3-5.0, table 12.2). 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 five year deferred treatment-free survival was 70.8% (figure 12.2). After deferred radical prostatectomy 1 man had capsular penetration (pT3A) and 4 had positive margins (table 12.3).

Table 12.2 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*
Active surveillance	*No.*	106	134	38	**278**	
Follow-up (years)	*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 yrs*	2 (2.2)	11 (9.2)	4 (17.4)	**17 (7.3)**	*0.02**
	2-4 yrs	9 (10.0)	20 (16.7)	3 (13.0)	**32 (13.7)**	
	4-6 yrs	23 (25.6)	20 (16.7)	2 (8.7)	**45 (19.3)**	
	6-8 yrs	14 (15.6)	8 (6.7)	1 (4.3)	**23 (9.9)**	
	8-10 yrs	6 (6.7)	7 (5.8)	0 (0.0)	**13 (5.6)**	
	>10 yrs	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 (months)	*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[1]	*5-yr*	87.2	91.9		**89.0**	*0.45****
PC-survival[1]	*5-yr*	100.0	100.0	100.0	**100.0**	

* *Chi-square Test*

** *Kruskal Wallis Test*

*** *Log-rank Test for trend*

AS *Active surveillance*

PSA DT *PSA doubling time*

Yrs *Years*

RP *Radical prostatectomy*

RT *Radiotherapy*

HT *Hormonal treatment*

PC *Prostate cancer*

N/a *Not available; less than three PSA values.*

[1] *Kaplan-Meier*

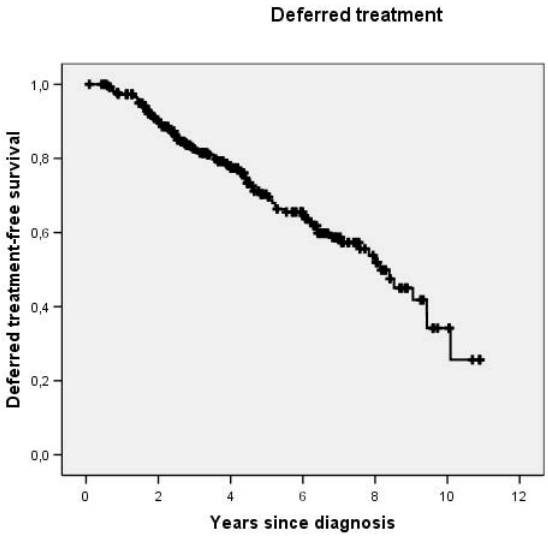

Figure 12.2 Kaplan-Meier projection of deferred treatment free survival (N=263)

Follow-up (yrs)	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

Table 12.3 Pathological 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)
Pathological stage	**pT2A**	1
	pT2C	9
	pT3A	1
	N1	0
Gleason score	**<7**	9
	=7	2
Margin status	**Positive**	4

25-75p 25th and 75th percentile

According to the 1992 TNM system

PSA doubling time

Table 12.4 shows that the initial PSA-level and the PSA doubling time, while not a predetermined reason for changing to deferred treatment, had a significant relationship with that decision, in contrast to the last PSA level before treatment. A total of 1,799 PSA tests were performed, with a median of 4 tests per patient (25-75p; 2-7 tests). The PSA doubling time was calculated for 234 men with 3 or more PSA tests. A PSA doubling time longer than 10 years or negative (i.e. PSA half-life) was noted in 21.4% and 22.6%.

Table 12.4 Prognostic factors for freedom of deferred treatment and death

		5-yr DTFS (%)	Log-rank
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 PSA*
5-yr DTFS *5-year deferred treatment free survival*
PSA DT *PSA doubling time*

Outcome

Twenty six men (9.4%) died during follow-up; none from prostate cancer. After 8 years, the prostate cancer-specific survival was 100.0% and the overall-survival was 84.0% (table 12.2). Forty three men (15.5%) were still at risk after 8 years; 26 (60.5%) of those had not received any treatment for their prostate cancer.

DISCUSSION

Of men diagnosed at the prevalence (i.e. first) screening of the ERSPC screening program, 10.2% were safely managed by active surveillance: during the median follow-up of 6 years 18.1% deceased; all of intercurrent diseases. Men diagnosed at repeated screening had more beneficial characteristics and were more likely to elect active surveillance. The latter either 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 longer than 10 years

or negative in 43.7% of cases. Although this 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 decease from other causes. Vis et al. 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.[209] Another step towards a more personalized risk prediction of potentially indolent prostate cancer is the development and use of nomograms.[12,210] The window of opportunity for active surveillance strategies is unknown, but based on 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.[109,110,181,186] Tumors which have a high probability to be indolent could appear to be important prostate cancers due to biopsy undersampling and dedifferentiation.[187] However, given the minimal improvement in cancer-specific survival when comparing surgical treatment to no treatment among men with cancers not detected by screening,[113] it seems unlikely that active surveillance of low-risk, screen-detected cancers will place patients at undue risk of an adverse outcome.[113] Two studies could not find adverse effects of prolonged delays on the outcome after radical prostatectomy for men enrolled in their active surveillance programs.[182,211] 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.[61] It would be a big advance if variables predicting anxiety in patients could be identified in order to risk stratify patients. Offering men a support program could be of help.[67] 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 mainly based on radical prostatectomy series and there is no direct evidence to support this relationship in the natural course of screen-detected prostate cancer.[212] McLaren et al. 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 ($P < 0.001$).[213] To further establish these correlations an evaluation of PSA kinetics on a proper endpoint is important. Due to 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 seven years, our cohort includes almost a quarter of men with doubling times under five years who show no signs of progression. In the cohort of Carter et al. the median PSA doubling time (DT) was 2.5 years for those who underwent therapy; those remaining on watchful waiting had a median DT of 25.8 years.[181]

Klotz et al. reported that in a cohort of 299 patients 65% remained free of treatment at 8 years, which is more than the 52.0% in our study.[186] During a follow-up of 3.8 years Carter et al. had ninety-eight patients who remained on watchful waiting; 215 proceeded to treatment.[181] A total of 57.3% and 73.2% chose treatment within the first 2 and 4 years, respectively. In our cohort 29% elected deferred treatment with a lower 4-year 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 years (range 10.8-12.1).[37] This means that men are diagnosed a mean 11.2 years before the cancer would be diagnosed clinically. An important proportion of these men is therefore eligible for active surveillance. We have to await the follow-up periods of 15 years 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 and no standard repeat biopsies were scheduled. There is evidence that detection rates increase with the number of cores.[214] More importantly, obtaining more cores results in more adequate sampling and allows for increased risk stratification.[215] 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 asses the value of a fixed active surveillance program has been initiated in Rotterdam (i.e. PRIAS). Although these measures were not implemented at the time of follow-up of this cohort, the oncological 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.

CONCLUSION

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 years. 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 for insignificant disease. Active surveillance seems to offer an important opportunity for the current overtreatment that results from screening.

PART V

GENERAL DISCUSSION

Chapter 13

Discussion

TOWARDS A CLINICAL POLICY FOR ACTIVE SURVEILLANCE

Natural course of screen-detected prostate cancer

The current knowledge of the natural history of prostate cancer is mainly based on clinically detected cases.[109,110,205] The available studies show histological grade to be the most important prognostic variable. In 1994 Chodak et al. concluded from a pooled analysis of 828 case records from six nonrandomized studies, that the strategy of initial conservative management and delayed hormone therapy is a reasonable choice for some men with grade 1 or 2 clinically localized prostate cancer, particularly for those who have an average life expectancy of 10 years or less.[205] Factors that had a significant effect on disease-specific survival were grade 3 tumors (risk ratio, 10.04), residence in Israel (risk ratio, 2.48) or New York (risk ratio, 0.37), and age under 61 years (risk ratio, 0.32). Ten years after diagnosis, disease-specific survival was 87 percent for men with grade 1 or 2 tumors and 34 percent for those with grade 3 tumors; metastasis-free survival among men who had not died of other causes was 81 percent for grade 1, 58 percent for grade 2, and 26 percent for grade 3 disease. These findings were not affected by the inclusion of men who had early-stage cancer, were older, had worse-than-average health, or underwent delayed radiation therapy or radical prostatectomy.

Johansson et al. have studied a cohort of 223 conservatively managed men who had organ confined disease at diagnosis.[109] If progression occurred, orchiectomy or exogenous estrogens were offered. After a median follow-up of 21 years 91 percent of patients had died; prostate cancer was the cause of death in 16 percent, while 40 percent had progression of disease. Again, poorly differentiated disease was the worst prognostic factor.

Data published by Albertsen et al. describe the survival of men with organ confined prostate cancer who were managed conservatively.[110] The 20-year prostate cancer specific mortality for men with a Gleason score smaller than 6 varies from 4 percent to 15 percent, according to age at diagnosis. Overall mortality is then determined by comorbidity. The majority of these men are currently treated with invasive procedures, which might not be needed.[49] Although the cause-specific mortality is 20 percent to 30 percent in men with Gleason score 6 tumors, in men with Gleason score 7 disease already 40-75 percent decease as a result of prostate cancer. Moreover are these men less likely to die from other causes. The population described by Albertsen et al. was diagnosed before PSA was introduced. Therefore, 60 percent of men were diagnosed by transurethral resection of the prostate (TURP). Categories T1a and T1b may have a different outcome which is not specified. As mentioned before, screening diagnoses prostate cancers earlier in their course, thus at younger age, and as a result the survival of men is likely to be longer.[37,44,46]

There is a lack of evidence concerning the differences in outcome between expectancy and treatment with curative intent for localized prostate cancer. From the Surveillance Epidemiology and End Results (SEER) database, several population-based studies towards the effect of treatment of clinically localized prostate cancer on the overall and disease-specific survival have been performed.[216,217] Lu-Yao and Yao published the data on 10-year survival of a cohort of 59,876 men.[216] The study showed that by the intention-to-treat approach, 10-year prostate-cancer-specific survival for grade 1 cancer was 94% (95% CI 91-95) after prostatectomy, 90% (87-92) after radiotherapy, and 93% (91-94) after conservative management. The corresponding survival figures in grade 2 cancers were 87% (85-89), 76% (72-79), and 77% (74-80); those in grade 3 cancer were 67% (62-71), 53% (47-58), and 45% (40-51). The authors did not test for significance of the differences formed and concluded that it was impossible to adjust for all confounding factors.[216] Therefore, the authors did not attempt to draw definite conclusions about treatment efficacies. In fact, they conclude that randomized controlled trials are needed to provide definitive information about the relative efficacy of prostate cancer treatments. However, Wong et al. performed a comparable study using the same SEER database to study the value of radical treatment compared to observation in older men with prostate cancer.[217] Although the impact of biases on the performed analyses has not changed over almost a decade, these authors conclude that observation is associated with a lower chance of overall survival than radical treatment. In both studies, observation implies that men are managed expectantly and offered hormonal treatment once progression occurs.

Only one study has randomized men between watchful waiting and radical prostatectomy. This study from the Scandinavian Prostate Cancer Group number 4 (Sprostate cancerG-4) showed that operated men had a slightly better survival after 8 years of follow-up.[113,218] The difference between the two groups in the cumulative incidence of death from prostate cancer increased over time, from 2 percentage points (95 percent confidence interval, –0.6 to 4.7) after five years of follow-up to 5.3 percentage points (95 percent confidence interval, –0.3 to 11.0) after 10 years, in favor of radical prostatectomy. The relative risk among men assigned to radical prostatectomy, as compared with those assigned to watchful waiting, was 0.56 (95 percent confidence interval, 0.36 to 0.88). Twenty patients had to be operated to save one death from prostate cancer. However, it was shown that men under 65 had larger effect differences. Although a longer follow-up would be very valuable, it is important to make two remarks with regard to the extrapolation of these data for judging the value of active surveillance. Firstly, watchful waiting should be clearly differentiated from active surveillance. While men were offered hormonal treatment in case of progression in the Sprostate cancerG4 study, men in active surveillance strategies discussed in this thesis should be fit for and must receive curative treatment in case of (suspected) progression. Currently ongoing studies have to show how important this difference in approach is.[186] The second important argument against the use of the Scandinavian trial as evidence for the application of radical treatment instead of

active surveillance is the baseline risk of men randomized. Participants were clinically diagnosed men who had a PSA at diagnosis of more than 10 ng/mL in 44 percent, a biopsy Gleason score higher than 6 in 39 percent and a clinical stage T3 or T4 tumor in 14 percent of cases. This is a relatively high-risk group of patients of which most would not be included in one of the present active surveillance studies. Even with these men included and not accounting for lead-time in currently detected cancers, only a small, but possibly significant effect difference of surgery might be shown. For all these reasons, a revaluation of the costs and benefits of immediate active treatment in the era of widespread screening is necessary: the number of patients needed to be treated is high, and the lead time to the onset of symptoms and treatment may be long in those undergoing monitoring, but the removal of small tumors may facilitate surgery and result in fewer side effects. There are no randomized controlled trials which compare radiotherapy with watchful waiting.

Early detection by PSA advances prostate cancer diagnosis in time (i.e. lead time).[44] For men aged 55–67 years lead time amounts to 12.3 years in a screening setting.[37] This lead-time is expected to be shorter for aggressive cancers and longer or even indefinite for indolent ones. Long-term outcome data on the natural course of screen-detected disease are not available, but will be provided by ongoing studies, such as the START trial, the ProtecT study and from PRIAS. The latter originates from Rotterdam and is in fact a spin-off from the ERSPC. More information about these initiatives can be found in the future perspectives section.

Deferred treatment

Outcome data for men on active surveillance are rare, but Klotz et al. have reported on their cohort of 299 men with a mean follow-up of 8 years.[186] Although only three men died from prostate cancer, the high proportion of advanced disease at the time of a deferred radical prostatectomy has been mentioned as a point of concern. However, these results are contrasted by the report of Warlick et al. from the Johns Hopkins group.[182] Their active surveillance program includes annual repeat biopsies and relies less on PSA kinetics for follow-up. The authors have compared outcomes of 38 patients with small, lower-grade prostate cancer in their expectant management program who underwent delayed surgical intervention at a median of 26.5 months (95 percent confidence interval (CI): 17 to 32 months; range: 12.0-73.0 months) after diagnosis with 150 similar patients who underwent immediate surgical intervention at a median of 3.0 months (95 percent CI: 2 to 4 months; range: 1.0-9.0 months) after diagnosis. After adjusting for age and prostate-specific antigen (PSA) density, the risks of non-curable cancer associated with delayed and immediate intervention did not differ significantly (relative risk=1.08, 95 percent CI = 0.55 to 2.12). Age, PSA, and PSA density were all significantly associated with the risk of non-curable cancer. They therefore concluded that delayed prostate cancer surgery for patients with small, lower-grade prostate cancers does not appear to compromise curability.

Also, Khatami et al. have conducted a case-control study to investigate the chance of radical cure after a delay in treatment because of active surveillance.[211] Tumor volume did not differ significantly between cases and controls: 1.35 vs. 1.05 cm (3), respectively. The frequency of extracapsular growth, Gleason score and time to progression after radical prostatectomy within a mean follow-up period of 2 years were also similar between the two groups. It was concluded that in selected patients with very early prostate cancer it seems that close surveillance followed by prostatectomy when signs of progression appear is a low-risk option.

The impact of a delay in treatment was addressed in a small retrospective study in the Rotterdam region as well, comparing men with immediate curative treatment to age matched men initially managed with watchful waiting followed by deferred curative treatment.[219] Of 261 men managed on watchful waiting, 27 (10.3 percent) received deferred treatment with curative intent, six with radical prostatectomy and 21 with radiotherapy. Most tumors had a Gleason score of 3+3=6 (77 percent). Median time of follow-up was comparable to the controls, and between 3 and 5 years for both treatment modalities. The outcome of the comparison with age-matched controls directly treated with curative intent was that biochemical progression rates were equal in both groups. This small retrospective study supports the hypothesis that deferring treatment in patients with selected, favorable prostate cancer characteristics does not influence the time of biochemical progression.

In order to cope with the large numbers of men currently (over)diagnosed with prostate cancer, it is an important research goal to risk stratify men whose prostate cancer is detected by screening and to subsequently offer them active surveillance. Therefore, efforts towards a standard clinical approach have to be made. Early detection causes a significant stage shift towards more locally confined and less aggressive cancers.[46] The long lead-time, stage reduction and natural history data cited above indicate that for properly selected cases there is a long 'time-window' during which active observation must be safe without losing the opportunity for cure. This is supported by evidence from nomograms, prognostic tables, and by the only available randomized study of observation against radical prostatectomy.[12,113,192,220,221]

Biopsy technique

Prostate cancer is generally diagnosed by an ultrasound (TRUS) guided prostatic biopsy. The current literature has not reached agreement about the optimal number of cores which should be taken. This not only holds for the detection of prostate cancers, but also for the reliability of risk-stratification based on pathological parameters, such as the amount of invaded tissue and the Gleason score. The majority of the publications on this subject indicate that a higher number of cores per biopsy results in the detection of more cancers.[83,199,203,222,223] There is only

one study which was not able to show a significant difference in cancer detection between 6 and 12 cores per biopsy.[224]

Undersampling is defined as the effect that the pathology based on tissue obtained by biopsy underestimates the tumor in grade, stage and/or size. The amount of undersampling can be lowered by increasing the number of biopsy cores. More intensive sampling (i.e. taking more biopsy cores) results not only in more, but also detects many cancers which are likely indolent and should not have been detected at all.[187] For sampling and for detection reasons, the number of biopsy cores has been increased in the last decade. A sextant biopsy used to be common in the nineties, when the ERSPC was initiated. Although the current number of biopsy cores varies widely by geographical region, sextant biopsies are now regarded on the lower end of the 'ideal' number of cores to be obtained. An extreme consequences of the desire for improved cancer detection and adequate sampling are saturation biopsies, which can include up to 54 cores.[187]

The size of the prostate also influences the probability of finding a tumor. Therefore, the size of the prostatic gland should be considered in determining the number of cores to be obtained. Vashi et al. have constructed a mathematical model to calculate the amount of cores needed to diagnose a tumor of certain size with 90 percent certainty.[203] For example: to diagnose a tumor with a volume of 1 cc in a prostate of 20 grams with a probability of 90 percent, a sextant biopsy would be sufficient, while 15 cores are needed to diagnose the same tumor in a prostate of 50 grams. With the increase of the size of the prostate, the detection rate of both the standard and the lateralized sextant biopsy decreases significantly. Eskicorapci show the additional value of 10 over 8 cores per biopsy in prostates larger than 35 grams.[225] Remarkably, findings at repeat biopsy correlated well with the presence of insignificant disease in a study by Stephenson et al.[226] It is realized that biopsy grading is associated with undergrading in 20 to 30 percent due to the nature of the sampling procedure.[176,227-230] This, however, might be compensated for in the strategy for monitoring. On the other side, 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.[187]

Patient selection

Criteria for selecting patients for active surveillance have not been established. Ideally, patients should be selected who either will not show disease progression during their lifetime or, if they show progression, will still be eligible for curative management with a high chance of success. Patients selected for active surveillance should be fit for surgery or radiotherapy if needed.

Regarding tumor stage, various authors have chosen locally confined, non-palpable and just palpable disease (T2a on digital rectal examination DRE) as entry criterion for their studies.[59,60] Carter et al. have shown in clinical series that with a pre-treatment PSA level greater than 5.0 ng/mL, 30 percent of 317 clinically detected cancers were non-curable (pT3). In the experience of the Rotterdam section of the ERSPC, a PSA of 8-10 ng/mL relates to 25 percent of pT3-4 cases. The absolute role of serum PSA levels may be limited in patient selection, because of prostate volume, the biological variation of PSA within and between patients is large, and because there is a poor correlation with tumor grade. Just like DRE. PSA density and free/total ratio need to be studied for their adjuvant value.

In the study of Postma et al. the clinical follow-up of men with minimal cancers was studied in a group of participants from the general population of the Rotterdam region.[147,197] This study described the incidence and follow-up of patients with clinical focal (minimal) prostate carcinoma in 2 screening rounds with an interval of 4 years. Focal carcinoma was defined as ≤3.0 mm involvement by tumor in 1 biopsy core on sextant biopsy, lacking Gleason pattern 4 or 5. The proportion of patients with focal prostate carcinoma increased significantly from 16 percent in the first screening round to 29 percent in the second screening round. In those treated with radical prostatectomy (108 out of 355), the median tumor volume was 0.16 mL. A PSA density cut-off level of ≤0.1 ng/mL/cmP^{3P} at the time of diagnosis predicted a minimal (<0.5 mL), organ-confined tumor in 94 percent of patients. The authors concluded that a considerable number of men with screen detected cancers have minimal disease. A low PSA, prostate volume, the number of positive cores, the grading, and the cancer length of prostate biopsies can predict minimal cancers with a high accuracy.

The prognostic value of the biopsy Gleason score has been shown to be the most important independent prognostic factor in multivariate analyses. It is therefore incorporated in all available nomograms.[175,192,228,231-233] A man with clinical stage T1 or T2 disease, a PSA-level of 10 ng/mL or less and a biopsy Gleason score 6 or less has a 98 percent chance not to die from prostate cancer in the next five years, according to the nomogram of d'Amico et al.[228] Although the Gleason score is currently the gold-standard for the grading of prostate cancer, the study by Vis et al, which is part of this thesis, found a superior predictive value of the proportion or length of high grade Gleason patterns in the biopsy.[209] Cheng et al. studied the same variable in radical prostatectomy specimens and corroborate with our findings.[156] However, Freedland et al. reported that the proportion of cancerous tissue and not the proportion of 4 and 5 tissue was most predictive of biochemical failure or adverse pathology.[234] More research into the feasibility of using the length of high grade cancer in the biopsy instead of the Gleason score is ongoing at our institution.

It is undisputed that men with a family history of prostate cancer have a higher risk to be diagnosed with this disease. The relative risk was 1.63 in our analysis based on men allocated to the screen-arm of the ERSPC. An effect of family history on the biochemical outcome could not be found. It was therefore concluded that although screened men 55 to 75 years old with a father or a brother having prostate cancer are at a substantially greater risk to be diagnosed with prostate cancer, the clinical presentation and prognosis by biochemical progression are not different compared to sporadic cases. The results of this analysis were contrasted by a more recent study of Kupelian et al.[131] The authors claim it to be the first study that demonstrates the presence of a family history of prostate cancer to correlate with treatment outcome in a large unselected series of patients. Their findings suggest that familial prostate cancer may have a more aggressive course than non-familial prostate cancer, and that clinical and/or pathologic parameters may not adequately predict this course. Thompson et al. studied the results from the Prostate Cancer Prevention Trial (PCPT) and found that a positive family history was associated with an increased risk for prostate cancer, but not for high-grade disease. It remains to be seen what the follow-up of this group of men reveals. Siddiqui et al reported that except for preoperative prostate specific antigen, clinico-pathological features and long-term oncological outcomes are equivalent after radical prostatectomy in patients with familial, hereditary and sporadic prostate cancer.[235] Recent reports confirm our findings of equal aggressiveness of men with familial and sporadic prostate cancer detected in the PSA era.[235,236] Family history is therefore solely a risk factor for a higher incidence of prostate cancer, but not for a higher risk of diagnosed cancers.

Follow-up

A fundamental question in prostate cancer research is whether screening with PSA just detects more tumors with favorable characteristics or if dedifferentiation is actually prevented by early detection and subsequent treatment. The latter option implies that tumors dedifferentiate in the preclinical screen-detectable phase. Although epidemiological evidence shows that dedifferentiation as a major mechanism of progression in prostate cancer, this key question is still heavily investigated.[45] Tumors dedifferentiate during the screen-detectable phase and consequently screening with PSA and early treatment can prevent further dedifferentiation. Various retrospective and prospective studies have addressed the evaluation of prognostic factors at entry relative to disease progression. The factors evaluated are 1) PSA and related derivatives like PSA-doubling time (PSA density), the ratio between free and total serum PSA (FT-ratio), and prostate size corrected PSA (PSA density), and 2) biopsy related information like biopsy grade, cancer length, and the number of positive biopsies. Comorbidity and age influence overall survival, but are not correlated to disease progression.[237-239] In two studies the initial PSA and PSA doubling time obtained during the follow-up correlated significantly with clinical progression.[59,213,226] In another study PSA density and F/T-ratio correlated well with disease progression, while the absolute annual PSA increase did not.[60,240] Zietman et

al. found that age was the most important determinant for remaining free from therapeutic intervention.[240]

In the studies published on watchful waiting,[59,60,213,226,240] most authors feel that patients should be followed at 3–6-monthly intervals, and 3-monthly during the first 1–2 years. A 3-monthly interval during the initial period of follow-up will provide many PSA values, which gives the opportunity to consider biological variation and to calculate the PSA density. All authors used DRE during the follow-up visits in order to detect progression. A repeat biopsy of 6-12 cores, either 6-monthly, yearly or 18-monthly, or on indication, was used to detect grade progression.[59,60,226,240]

Parameters for initiating treatment have been shown to be arbitrary, and are often governed by uncertainties and the patient's psychological stress. The candidate criteria identifying those cases that tend to progress to a potentially incurable stage, are clinical stage (by DRE), PSA-increase (expressed in PSA density), grade progression (by repeat biopsy), and increase of tumor volume (as indicated by the number of positive repeat biopsies, or the tumor length in cores). In order to assess PSA changes over time adequately, many observations over a period of ≥ 2 years are necessary to take account of the biological variation of serum PSA when calculating PSA velocity and doubling times.[241] Several groups have addressed the best way of determining PSA increases and there seems to be a growing consensus that PSA-DT is the most suitable variable.

All considerations of PSA-change over time are based on the assumption that PSA levels correlate with tumor mass, as has been found in some reports,[242,243] but questioned lately.[244] Although there is a weak correlation between tumor mass and the absolute level of pretreatment PSA, PSA changes as expressed in PSA density appear to correlate significantly with clinical progression,[241,245] especially in early stages when no endocrine manipulations have been made. PSA doubling time is defined as the time PSA needs to double its start-value. To preserve a difference in men who for example have a PSA of 2 and 10, the 2logPSA should be used. The PSA doubling time can subsequently be calculated by 1/slope. The slope denotes the slope through all 2log PSA values.

The use of PSA doubling time as a decision tool is based on the observation that preoperative PSA levels are significantly correlated with the tumor volume in radical prostatectomy specimens.[243] It is furthermore based on the knowledge that PSA values have an exponential course in individual non-treated patients.[242] The PSA doubling time should therefore be a straight line in a log-plot.[183] It is intuitively correct that the PSA doubling time is a good indicator for tumor growth, and this assumption is supported by studies which show that PSA doubling time is a strong predictor for the risk of metastases and death due to prostate cancer after

radical prostatectomy or radiotherapy.[246,247] McLaren et al. have shown that the PSA doubling time was the strongest predictor of clinical progression in conservatively treated men.[213] Klotz described that in his active surveillance cohort the metastases free survival was 99 percent after 8 years. Initially, a PSA doubling time of less than two years led to curative treatment.[183] Khatami et al. have a significant relationship between the PSA doubling time and the biochemical control in men who received a deferred prostatectomy.

If a given prostate cancer is indeed clinically insignificant, the doubling time will be more alike that of men without prostate cancer.[248] Prostate cancer with a PSA doubling time < 3 years is thought to have a poor prognosis. The 3 to 10 years range is unclear and needs further study. To minimize the chance of local progression, it is therefore advisable to perform a repeat biopsy during this time. A PSA doubling time longer than ten years suggests an indolent prostate cancer and therefore there is no need for a repeat biopsy. Clinical progression in locally confined disease with no in crease of PSA seems to be extremely rare. The PSA density during watchful waiting is extremely variable due to the presence of benign hyperplasia, and ranges between less than 2 years to over 50 years.[249] When less than 4 years, disease progression by T-stage was reported in 27 percent of men on watchful waiting.[226] A strong correlation between PSA doubling time and clinical progression was also observed in the study of McLaren in which men on watchful waiting were stratified according to PSA density.[213] Those with no PSA doubling time progression also did not show clinical progression, while all men with a PSA doubling time of less than 1.5 years progressed within one year. The utility of PSA doubling time needs to be established further.

The DRE has a high interobserver variability.[59] In the different active surveillance studies, different thresholds for the clinical stage are used.[59,60,250] The correlation between progression measured by DRE and that by PSA density is low.[226]

In conclusion, patient selection, follow-up and trigger points for treatment are still under investigation. Significant recent progress has however been made which allows the set-up of large scale studies.

Chapter 14

Epilogue

FUTURE DIRECTIONS

Based on the presented data and on the literature review provided in the general discussion of this thesis, a prospective, observational active surveillance study has been initiated. This research endeavor has been named Prostate cancer Research International on Active Surveillance (PRIAS) and its outlines are described in this chapter. There is an internationally growing interest in the study of the natural course of the disease and the management of men with low-risk prostate cancer by active surveillance. Investigators from the British Columbia Cancer Agency (BCCA) and the University hospital of Helsinki (HYKS) have shown interest to collaborate intensely by sharing a centralized database based on the protocol and web-tool constructed in Rotterdam.

The PRIAS-project will deliver:

- A web-based decision tool for active surveillance
- Evidence based guidelines (protocol) for active surveillance
- A longitudinal biomaterial bank
- A database of active surveillance participants
- A calculator for risk of progression
- Insight in health related quality of life (HRQoL) effects of active surveillance
- Risk factors for increased anxiety and choice of deferred active therapy for reasons unrelated to progression of prostate cancer

Internet-based monitoring and decision tool

The website www.prias-project.org has been created for this study. It includes an information portal as well as an internet-based web-tool to facilitate and support clinicians to include and manage their active surveillance patients. The web-tool connects to an individual patient data files, which is password protected, and can only be entered by the physician, and by the data monitor of the study for quality control. This instrument is user-friendly and requires minimal handling in order to improve patient inclusion and follow-up compliance. Individual patient data are related to the protocol that supports monitoring and treatment decisions at every date of entry of follow-up data. The web-tool indicates the parameters used for decision making for the continuation of a patient on active surveillance, or for a change towards active treatment. All data entered into the web-tool become available in a structured database and will therefore be available for research.

The PRIAS protocol is divided into three parts: the biopsy protocol, the inclusion criteria and the follow-up protocol.

Biopsy protocol

Based on the available literature, we created a biopsy protocol which has already been introduced at our institution. In men with prostates smaller than 40 mL eight cores are obtained, in prostates 40-60 mL ten cores and in men with a gland larger than 60 mL 12 cores are taken. The reported undergrading of 20-30% is also compensated by the strategy for monitoring: repeated biopsies are included for follow-up.[176,227-230,251]

Eligibility (entry criteria)

A maximum PSA-level of 10 ng/mL was chosen in combination with a PSA-density limit of 0.2 ng/mL/mL in order to correct for the influence of benign prostatic hyperplasia (BPH) at increasing age and with repeated screening.

The definition of active surveillance implies that included men should be fit to receive curative treatment at any time during their disease. This implies that men should have an organ confined (clinical stage T1c or T2) prostate cancer at the time of inclusion.

Not only the proportion of cancer invasion in the biopsies, but also the number of cores invaded with prostate cancer can be of help in the decision which treatment should be applied.[234,252-254] The criteria of Epstein et al. use the proportion of prostate cancer in the biopsy as well; they found that men with a Gleason score ≤ 6, with two or less biopsies positive for prostate cancer with less than 50% invasion have a high probability (79%) to have a minimal focus of prostate cancer (≤ 0.5 mL).[176,177] this requires that every core is analyzed separately by the pathologist.

Inclusion criteria for the PRIAS study are:

- Patient should be fit for curative treatment
- PSA-level at diagnosis 10 ng/mL or less
- PSA density (PSA D) less than 0,2
- Clinical stage T1C or T2
- Adequate biopsy sampling
- One or 2 biopsy cores invaded with prostate cancer
- Gleason score 3+3=6 (or less)
- Participants must be willing to attend the follow-up visits

Exclusion-criteria:

- Patient can not or does not want to be irradiated or operated
- A previous therapy for prostate cancer

Follow-up protocol

Taking all information into account alluded to earlier in the discussion of this thesis, recommendations regarding a balanced policy for monitoring and treatment indications can be made.[255]

Frequency of visits

It is unnecessary to calculate the PSA DT with every new PSA recording. The biological variation in serum PSA necessitates that calculation of PSA DT is based on several measurements. For this reason annual evaluations are recommended. At the end of the first year, an evaluation on biochemical, clinical and histological progression can be made. By the end of the second year, the evaluation is based on at least DRE and PSA DT.

The argument for choosing a 3-monthly visit-schedule in the first two years and a semi-annual schedule thereafter is to recognize and filter out the fast growing tumors, which are not corresponding with the definition of clinically irrelevant tumors. Those are likely the tumors that were undersampled at diagnosis. By means of repeat biopsy, four PSA measurements and two DREs in the first year during the follow-up, men who have aggressive cancers should be identified. They would then have a therapy delay of a year. Most reports in the literature do not show a negative effect for this delay.[250,256-259]

The proposed pattern for repeat biopsies is a one, four, seven, ten, fifteen and twenty years biopsy scheme. These moments are arbitrary, but do corroborate with the randomized controlled study of radical prostatectomy versus active surveillance START study. The number of biopsy cores is again indicated by our biopsy protocol. Besides the standard biopsies, a repeat biopsy is necessary if the PSA doubling time is between three and ten years. No more than one biopsy per year should be obtained. Repeat biopsy after 12-18 months often shows no cancer at all,[260] but when upgrading is present, this may be the result of having missed the less differentiated parts in earlier biopsies. Upgrading therefore should be regarded as an indication for active treatment.

Decision parameters

PSA-doubling times, histology by repeat prostate biopsy, and clinical stage assessed by DRE are considered to be criteria for follow-up and change towards active therapy. For identical reasons, changes in PSAD and FT-ratio were chosen as parameters that need further study within this protocol.

During the first two years, three-monthly PSA determinations are needed to reliably calculate the PSA doubling time with at least three (but better four) values. A cut-off level of 3 years was

chosen in line with the most extensive active surveillance study on clinical cases performed so far by Klotz in which the cancer-specific survival at 8 years was 99,3 %.[186]

It is realized that small alterations on DRE might be the result of previous biopsy procedures or interobserver variability.[14]

Any indication of the presence of a larger (but previously missed) tumor, or a growing or multifocal tumor by an increase in the number of positive biopsies cores will be taken as an indication to advise curative treatment. The same is true for any increase of the Gleason grade that might be the result of understaging or dedifferentiation over time. The small decreases of understaging that saturation biopsies (more than 20 core samples) might give at the time of study entry are not considered to be in balance with the increase of patient discomfort that results from such an extra procedure.[187]

Nomograms

It is likely that in the near future nomograms will be used for the selection and follow-up of active surveillance participants instead of fixed criteria. The Kattan nomogram for the prediction of indolent prostate cancer has been updated and recalibrated with the use of our cohort of screen-detected patients in whom a radical prostatectomy was performed.[12,220] Although the Steyerberg nomogram has not been validated on clinical endpoints yet, it is very well possible that a certain probability for indolent cancer will serve as a cut-off for the eligibility of active surveillance programs. For example, for a 70% or higher probability of indolent disease using the Steyerberg risk indicator could prompt patients and doctors to consider active surveillance. With the help of nomograms a custom-made risk profile is available that can reassure men in their choice for active surveillance.

Quality of life

It is known from the scarcely available studies that anxiety in patients is an important reason for choosing deferred curative treatment. This study provides the possibility of investigating this issue further by adding a quality of life component.

Shortly after entering the active surveillance protocol, baseline HRQoL and potential determinants of unfavorable HRQoL while being on active surveillance and of a shift to active treatment without medical reasons will be assessed. Factors assessed as potential determinants of unfavorable HRQoL include:

- Demographic characteristics (e.g. level of education)
- Personality characteristics (we will use Eysenck Personality Questionnaire – revised Short Form[261]);

- Knowledge of localized prostate cancer and of effectiveness of treatment options (approx. 10 items based on Nijs, Essink-Bot et al.[262]);
- 'Risk perception': estimation of own risk of disease progression, and perceived seriousness of this risk (3 items, based on Van Dooren et al[263], and Kruijshaar et al[264])
- Decisional conflict (with the adaptations to assess decisional conflict regarding prostate cancer treatment choice as proposed by Steginga et al 2004 (uncertainty about prostate cancer; men's satisfaction and confidence with their treatment decision)[65,265]

At baseline and during follow-up, HRQoL will be assessed by:
- prostate cancer-specific quality of life: EPIC[266]
- Generic HRQoL: SF-12 [267]
- Mental health: STAI-state (6-item version)[268], CES-D [269], Impact of Event scale[270]; prostate cancer-specific anxiety[271]

The measures for the last three variables are chosen to allow for comparison of the data with data from patients who were actively treated by radical prostatectomy (radical prostatectomy) or external beam radiotherapy.[40,272,273] The measures also follow recent reviews such as Penson et al., and international studies such as Steginga and Roth.[65,146,271]

The HRQoL study will include biannual follow-up in the first two years and annual follow-up afterwards for the duration of the study. Follow-up assessments will include decisional conflict and HRQoL. Follow-up data will be collected irrespective of whether the patient elected active therapy or not (data collection following 'intention to treat' principle).

In addition to the regular (bi)annual HRQoL assessments, patients who are referred to active treatment will be interviewed by telephone to explore the feelings of the patient around the deferred treatment. In case of a choice for active treatment for other reasons than disease progression (as defined in the study protocol), the reasons for change of therapy are explored.

Analysis of HRQoL data will be directed at:
- Description of HRQoL over time (repeated measures analysis of variance), both for the group as a whole and by subgroup (those still on active surveillance versus those with deferred active therapy).
- Comparison with HRQoL data of patients who underwent radical prostatectomy and external beam radiotherapy.[272,273]
- Analysis of associations of baseline characteristics (demographic characteristics, personality characteristics, knowledge, risk perception, decisional conflict) with unfavorable HRQoL scores at later time points, and with a shift to active treatment for non-medical reasons.

A prognostic model to predict 'referral to active treatment'

Potential practical applications of the results of these analyses include (a) the selection of patients for active surveillance: if groups can be identified who are at high risk of negative HRQoL effects of being on active surveillance, this information may be used in the interaction between doctor and patient when discussing treatment options for localized prostate cancer; and (b) the potential of offering psychosocial support to men on active surveillance who are at high risk of unfavorable HRQoL or for shifting to active treatment without medical reasons. Hence, the results of the HRQoL study will contribute to prevention of unfavorable HRQoL and/or 'unnecessary' active treatments of localized prostate cancer.

Psychosocial interventions with favorable effects on HRQoL among patients with localized prostate cancer are found in the literature, see e.g. Penedo et al., Steginga et al. and Daubenmier et al.[67,274,275]

Endpoints

The main endpoints for the PRIAS study are:

- Percentage of disease progression as indicated by a change of parameters
- Time to disease progression

Secondary endpoints are:

- The number of men on active surveillance as a proportion of the total number of prostate cancers detected in a region
- The number of men who shift from active surveillance to active treatment
- Median time to treatment
- Treatment modality
- Outcome of treatment (staging, grading)
- Reason for treatment alterations
- Quality of life,
- (Time to) overall death
- (Time to) prostate cancer death

Other research initiatives

Prostate testing for cancer and Treatment (ProtecT)

The ProtecT study is an ongoing, multi-centre, randomized trial of treatments for localized prostate cancer in which asymptomatic men aged 50–69 years in nine parts of the UK (Birmingham, Bristol, Cambridge, Cardiff, Edinburgh, Leeds, Leicester, Newcastle and Sheffield) are invited for prostate cancer testing. Men diagnosed with localized prostate cancer are asked to consent to a three-arm treatment trial of prostatectomy, radiotherapy or active monitoring (i.e. active surveillance). The study is open for recruitment from June 2001 until May 2008.

The overall aim is to evaluate the effectiveness, cost-effectiveness and acceptability of treatments for men with localized prostate cancer within the context of a pragmatic randomized controlled trial. Specific objectives are as follows:

1) To assess survival at 5, 10 years and 15 years following treatment

2) To investigate a number of short and medium-term outcomes, including: disease progression (biochemical and clinical), treatment complications, lower urinary tract symptoms, psychosocial impact of case-finding and treatment, including generic health status, quality of life and sexual function

3) To estimate the resource use and costs of case-finding, treatment and follow-up, and to compare costs and outcomes of treatment in terms of survival and health related quality of life.

4) To collect material suitable for basic science research, and develop a network for collaborative research.

Standard Treatment Against Restricted Treatment (START)[191]

In this trial, patients with favorable-risk disease are randomized between active surveillance and the patient's choice of standard therapy (surgery, brachytherapy, or external beam). The end point is prostate cancer–specific mortality. The trial will be implemented by the Clinical Trials Support Unit of the National Cancer Institute of the USA. Randomization should start in the beginning of 2007.

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Summary

The *first part* of this thesis includes a historical overview (**chapter 1**) and an introduction (**chapter 2**) to the problems which are encountered by prostate-specific antigen (PSA) screening for prostate cancer. It provides an introduction to the "European Randomized study of Screening for Prostate Cancer (ERSPC)". It furthermore describes the uncertain effect of the screening test, as well as its side-effects, of which overdiagnosis with subsequent overtreatment causes most concern. The scope of this thesis (**chapter 3**) assumes that the detection of low-risk overdiagnosed cancer can at present not be avoided. Therefore, based on current literature, including the reports from this thesis, a strategy called active surveillance has been developed.

The *second part* of this thesis deals with *effects of screening for prostate cancer*. **Chapter 4** compares the preliminary outcome of cancers detected in the screen and the control arm of the Rotterdam section of the ERSPC by means of biochemical progression rates. Although significantly more cancers were detected in the screen than in the control arm (1,339 vs. 298), their clinico-pathological features were more favorable. Furthermore, screened men had higher 5-year biochemical progression-free survival rates after surgery (84.4% vs. 58.9% in controls), radiotherapy (71.0% vs. 58.0%), and endocrine therapy (40.5% vs. 16.3%). The higher biochemical progression-free survival can at least in part be explained by stage migration related to lead and length-time. How screening will affect the mortality remains unclear.

Chapter 5 illustrates how PSA screening has changed the characteristics of the disease prostate cancer. It provides outcomes of two cohorts of men from two well-defined geographical areas diagnosed with prostate cancer and exposed to different intensities of prostate cancer screening. A cohort of 822 men from the screen arm of the ERSPC was compared to 947 men in a non-screened, non-randomized cohort, who were diagnosed with prostate cancer between January 1989 and December 1997 in a geographically neighboring region. The five- and ten year overall survival rates were higher in the screened cohort than in the non-screened cohort (88.8% versus 52.4%, and 68.4% versus 29.6%, respectively; $P<0.001$). Significant differences in survival were seen for all age-, stage-, and grade subgroups, except for metastatic disease at diagnosis. The impact of lead time and overdiagnosis on overall sur-

vival could not be assessed, but is expected to be the main cause of the observed differences between the two cohorts.

Since the beginning of the ERSPC, the use of PSA as a screening tool has become increasingly prevalent in the general population and therefore also in the control arm of the study (i.e. contamination). **Chapter 6** presents a feasibility study and an explorative simulation of the impact of adjusting for contamination and non-compliance according to Cuzick et al. (Stat med 1997) applied to the Rotterdam section of the ERSPC. A secondary analysis conducted with such adjustments allows to estimate the effect of screening in those men who comply with all aspects of screening; it gives an answer to the question "what happens to me if I get screened". The intention to screen analysis allows to judge the effect of a screening program applied to the general population. This simulated secondary analysis assumes reductions in prostate cancer mortality as endpoints but utilizes actual data of non-compliance and contamination by PSA use in ERSPC Rotterdam. Of the men allocated to the screen arm, 27.1% were noncompliant. In the control arm, 6,499 men (30.7%) had their PSA measured by a general practitioner for various but undetermined reasons (i.e. contamination). For a scenario in which the intention-to-screen analysis was assumed to show a decrease in prostate cancer mortality in the screened men of 6.7%, the secondary analysis based on those willing to accept their randomized allocation resulted in a decrease of 16.1% for those actually screened. Adjustment for non-compliance and contamination was shown to be feasible in this prostate cancer screening trial. It can therefore be used to carry out a secondary analysis in ERSPC Rotterdam and in ERSPC as a whole.

The *third part* of this thesis provides insight into *the risk-stratification of screen-detected prostate cancers*. **Chapter 7** illustrates that a family history of prostate cancer is an important risk factor for finding prostate cancer at biopsy. The clinical presentation and prognosis of familial disease remain uncertain. These parameters were evaluated in the first and second rounds of ERSPC Rotterdam. Information regarding the family history was obtained by a self-administered questionnaire from all participants at baseline. In the prevalence screen the cancer detection rate in 1,364 men (7.1%) with a positive family history was 7.7% (106 cancers in 1,364 screened men with a positive family history) while the positive predictive value of the biopsies was 32.2% (154 cancers of 532 biopsies). In 12,803 sporadic cases the detection rate was 4.7% and the positive predictive value was 23.6% ($p < 0.0001$ and 0.003, RR 1.63). No clinico-pathological differences were found between the two groups in the 1,559 men diagnosed in the first and second rounds. The overall biochemical progression-free survival rate after a mean follow-up of 56.8 months (range 0 to 129.9) was 76.8%, and was not significantly different in familial and sporadic cases ($p = 0.840$). These findings were consistent for the specific treatment modalities as well. Thus, although screened men aged 55 to 75 years diagnosed with prostate cancer who have a father or a brother with prostate cancer are at a

substantially greater risk, the clinical presentation and prognosis by biochemical progression are not different compared to sporadic cases.

Screening for prostate cancer has not only led to a stage migration, but also to a higher incidence. A decrease in mortality has occurred in several countries during the same time period. Risk stratification of screen-detected cancers at diagnosis has become important for the anticipation and interpretation of changing incidence and incidence-to-mortality ratios. **Chapter 8** contributes to the extreme side of the risk spectrum: the predictors of metastatic disease. From 1993 to 1998, 633 men were diagnosed with non-metastatic prostate cancer in the prevalence screen of the Rotterdam section of ERSPC. During the median follow-up of 7.5 years, 41 men developed metastatic disease. After 10 years the metastasis-free survival rate was 89.6%, the overall survival 64.7%. In a Cox model 2logPSA, biopsy Gleason score and the number of biopsy cores with prostate cancer were independent predictors for the development of metastases; the latter only predicted metastases that presented within 60 months of follow-up. The metastasis-free survival of men with prostate cancer detected in our prevalence screen was high. Whether this is related to the beneficial effects of screening or to overdiagnosis due to screening (or both) remains unclear. The prognostic factors known for clinically diagnosed disease also hold for screen-detected disease.

The stage and grade shift of currently diagnosed prostate cancer has led to a diminished prognostic power of the Gleason score system. We investigated the predictive value of the amount of high-grade cancer (Gleason growth patterns 4/5) in the biopsy for prostate-specific antigen (PSA) and clinical relapse after radical prostatectomy (**chapter 9**). PSA-tested participants (N=281) of ERSPC who underwent radical prostatectomy were analyzed. Besides clinical features and serum-PSA, histopathologic features as determined in the diagnostic biopsy and matching radical prostatectomy specimen were related to patient outcome. At a median follow-up of 7 yr, 39 (13.9%), 24 (8.5%), and 12 (4.3%) patients had PSA≥0.1 ng/mL, PSA≥1.0 ng/mL, and clinical relapse after radical prostatectomy, respectively. Using Cox proportional hazards, PSA level (p=0.002), length of tumor (p=0.040), and length of high-grade cancer (p=0.006) in the biopsy, but not Gleason score, were independent prognostic factors for biochemical relapse (PSA≥0.1 ng/mL) when assessed as continuous variables. In radical prostatectomies, the proportion of high-grade cancer (p<0.001) was most predictive of relapse (PSA≥0.1 ng/mL). For PSA≥1.0 ng/mL and clinical relapse, the amount of high-grade cancer, both in the biopsy specimen (p=0.016 and p=0.004, respectively) and radical prostatectomy specimen (p=0.002 and p=0.005, respectively), but not Gleason score, was an independent predictor. In biopsy and radical prostatectomy specimens of surgically treated prostate cancer, the amount of high-grade cancer is superior to the Gleason grading system in predicting patient outcome. We propose that, in addition to the Gleason score, the amount of Gleason growth patterns 4/5 in the biopsy (whether absolute length or proportion) should be included in the pathology report.

The objective of **chapter 10** is to determine what proportion of screen-detected cancers are indolent and can be considered for active surveillance. Nomograms provide predictions for individual patients based on multivariate analyses of large patient cohorts. These are likely to provide the best mechanisms for the selection of candidates for active surveillance strategies, because they are focused on individual patients rather than groups of patients. The Kattan et al. nomogram for the prediction of indolent prostate cancer has been validated and re-calibrated for use in a screening setting. That nomogram was used to calculate the number of men who were predicted to have indolent cancer in a screen-detected cohort from the Dutch section of the European Randomized study of Screening for Prostate Cancer (ERSPC). Eligibility criteria for nomogram use were: 1) clinical stage T1C or T2 disease, 2) PSA 20 ng/mL or less, 3) primary and secondary Gleason grade at most 3 in any biopsy core, 4) positive cores 50% or less, 5) total cancer in biopsy cores 20 mm or less and 6) benign tissue in all cores 40 mm or more. Of 1,629 prostate cancers detected in two subsequent screening rounds 825 were eligible for nomogram use. A total of 485 men (485 / 825 = 59%) were predicted to have indolent prostate cancer, which is 30% (485 / 1,629) of all screen-detected cases. Cancers found at repeated screening after four years had a higher probability of indolent prostate cancer than cases from the prevalence screening (44% vs. 23%; P<.001). With the help of this nomogram substantial groups of screen-detected prostate cancers can be identified which are likely to be indolent and can therefore be considered for active surveillance.

Opportunistic screening for prostate cancer has resulted in an increasing incidence in the Netherlands and many other parts of the world. For ethical, medical, and economic reasons it is necessary to decrease overdiagnosis and overtreatment and to define which patients can be managed by active surveillance. In the *fourth part* of this thesis, *active surveillance* was studied *as a way out of the overdiagnosis dilemma*. For the study in **chapter 11**, men with criteria that reflect current active surveillance studies were selected: those with a biopsy Gleason score ≤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. 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 years 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 active surveillance changed to definitive treatment during follow-up. Only three men died of prostate cancer, none of these were on active surveillance. Our observations provide preliminary validation of the arbitrary selection criteria for active surveillance.

Chapter 12 describes the PSA changes in a cohort of men from the ERSPC that initially were managed with active surveillance for prostate cancer. In this group, the PSA changes with time were studied in 278 patients with histologically proven prostate cancer, clinical stage T1c or

T2, a PSA-level 15 ng/mL or less and a biopsy Gleason score less than 8. The choice for watchful waiting was based on patients' wish or physicians' advice. PSA slope and PSA doubling time (PSA DT) were calculated in patients with three or more PSA test results available (N=233). Mean age at diagnosis was 70 years and the median PSA was 3.6 ng/mL. Of the patients 94.2% had a Gleason score of 3 + 3 or lower and 44.2% had a negative PSA doubling time or a doubling time longer than 10 years. It can be concluded from this study that in screen-detected prostate cancer a considerable subset of men show stable or even decreasing PSA values with time, and that this group of men have long PSA doubling time of more than 10 years. These males profit from an active surveillance policy with delayed treatment.

The *fifth part* of this thesis gives a literature overview and puts the described chapters into perspective. It furthermore describes the evidence which forms the basis for a prospective study which is for a large part based on this thesis: the PRIAS-project (Prostate cancer Research International: Active Surveillance), which is described in the epilogue. We hope to establish evidence-based guidelines for the management of clinically indolent cancer, which would allow to limit active treatment to those who need it and would reduce the harmful side effects of early detection. We will make a web-based decision tool available for proper selection and active surveillance that will contribute to prevent overtreatment of indolent prostate cancer and reduce health care costs. Future candidate prognostic factors can be tested in a carefully built database and biorepository. Our study will allow to identify men at risk of 'unnecessary' active treatment and allow the identification of subgroups who may be offered additional psychosocial support. If successful, the results can be incorporated in a modeling analysis of cost and effects (MISCAN) of screening policies in the Netherlands.

Samenvatting

Deel 1 van dit proefschrift geeft een overzicht van de historie van prostaatkankeronderzoek en haar behandeling (**hoofdstuk 1**). **Hoofdstuk 2** geeft een introductie in de gevolgen en de problemen van vroegopsporing naar prostaatkanker. Het is onbekend of vroegopsporing leidt tot een reductie in het aantal prostaatkankerdoden. Wel is duidelijk dat vroegopsoring leidt tot een forse toename van het aantal nieuw-gediagnosticeerde prostaatkankers per jaar (incidentie). Momenteel is er geen screeningsmethode beschikbaar waarbij alleen de potentieel gevaarlijke kankers gedetecteerd worden. In de doelstelling van dit proefschrift (**hoofdstuk 3**) wordt uitgelegd dat de huidige situatie, waarin al deze ongevaarlijke kankers worden gediagnosticeerd, voor dit moment wordt geacepteerd. Deze situatie van overdiagnose is de uitgangssituatie van dit proefschrift. Overdiagnose leidt dikwijls tot overbehandeling. In dit proefschrift wordt een methode beschreven waarbij het gerechtvaardigd is om bij geselecteerde kankers af te wachten met behandelen. Uit de gerandomiseerde screeningstudie voor prostaatkanker (ERSPC) is berekend dat ongeveer 50% van de vroeg ontdekte prostaatkankers zeer klein en weinig aggressief zijn en waarschijnlijk nooit zullen leiden tot symptomen. Deze kankers zouden dan ook niet behandeld moeten worden, tenzij ze tijdens het vervolgen tekenen van groei vertonen. Een dergelijk afwachtend beleid wordt 'active surveillance' genoemd.

In *deel 2* van dit proefschrift wordt het onderzoek beschreven naar de effecten van vroegopsporing naar prostaatkanker. **Hoofdstuk 4** vergelijkt de overleving van mannen in de interventie-arm van de ERSPC met de controle-arm. Het eindpunt voor deze studie was biochemische progressie. In de interventie arm van het Rotterdamse gedeelte van de ERSPC werden 1.339 prostaatkankers gevonden, terwijl in dezelfde periode slechts 298 kankers werden gediagnosticeerd in de controle arm. De klinische en pathologische parameters waren echter gunstiger in de interventie groep. Dit resulteerde ook in een betere biochemische progressie-vrije overleving, zowel na prostatectomie, na radiotherapie als na hormonale behandeling. Deze uitkomsten kunnen in ieder geval gedeeltelijk verklaard worden door het feit dat vroegopsporing kankers eerder in hun beloop vindt. Uit deze studie kan niet worden geconcludeerd of vroegopsporing de sterfte reduceert.

Hoofdstuk 5 illustreert dat de komst van PSA en het gebruik ervan in het kader van vroegopsporing de ziekte prostaatkanker in belangrijke mate heeft veranderd. In dit hoofdstuk worden mannen met prostaatkanker uit de interventie-arm van de ERPSC Rotterdam

(N=822) vergeleken met een groep mannen met prostaatkanker uit Zeeland welke in dezelfde periode werden gediagnosticeerd (N=947). Bekend was dat de intensiteit van PSA vroegopsporing in Zeeland laag was. Mannen in het Zeeuwse cohort hadden veel verder gevorderde ziekte ten tijde van diagnose. De 10-jaars overleving was significant hoger in de gescreende groep dan in het Zeeuwse cohort (68.4% versus 29.6%). Met uitzondering van metastasen op afstand bleven deze verschillen ook bestaan na correctie voor leeftijd, stadium en differentiatiegraad. Op basis van deze studie is het niet mogelijk om uitspraken te doen over het effect van vroegopsporing, maar wel over het veranderde gezicht dat prostaatkanker als gevolg van vroegopsporing heeft gekregen.

De uitkomsten van de ERSPC zullen gebaseerd zijn op een intention-to-screen analyse waarin de sterfte van de hele groep mannen die gerandomiseerd werd in de interventie arm wordt vergeleken met de sterftecijfers van de hele groep mannen in de controle arm. Echter, er zijn ook mannen in de interventie-arm die niet bereid zijn deel te nemen aan het hele screeningsalgoritme. Bovendien is sinds het begin van de ERSPC in 1993 het gebruik van de PSA-test in de algemene bevolking en dus ook in de controle arm van de ERSPC fors toegenomen. **Hoofdstuk 6** bevat een haalbaarheidsstudie naar het toepassen van een secundaire analyse op de ERSPC. In een secundaire analyse wordt gemeten wat het effect is van vroegopsporing in die mannen die bereid zijn deel te nemen aan het vroegopsporingsalgoritme. Een dergelijke analyse corrigeert voor het gebruik van PSA in de controle arm en het corrigeert voor non-participatie in de interventie-arm. Van alle mannen in de interventie-arm nam 27.1% niet aan het gehele vroegopsporingsprogramma deel. In de controle-arm liet 30.7% van de deelnemers een of meerdere PSA's bepalen door een huisarts. In een scenario waarin de primaire analyse van de ERSPC een sterftereductie zou geven van 6.7%, zou de secundaire analyse op 16.1% uitkomen voor die mannen die daadwerkelijk gescreend werden. Geconcludeerd kon worden dat een dergelijke secundaire analyse van de ERSPC belangrijk en uitvoerbaar is.

Het *derde deel* van dit proefschrift bevat uitkomsten van onderzoek naar de risico-stratificatie van door vroegopsporing gevonden prostaatkankers. Vroegopsporing naar prostaatkanker heeft niet alleen geleid tot een stadium migratie, maar ook tot een hogere incidentie. Bovendien is de sterfte aan prostaatkanker nagenoeg gelijk gebleven, of zelfs licht gedaald. Het is daarom steeds belangrijker geworden om het risico dat iedere kanker met zich meebrengt goed in te kunnen schatten. In **hoofdstuk 7** is de waarde van een positieve familieanamnese op het voorkomen en de prognose van prostaatkankers onderwerp van studie. Op basis van data uit de eerste twee onderzoeksrondes van de ERSPC Rotterdam kon worden geconcludeerd dat het hebben van een vader en/of een broer een risiscofactor is voor het krijgen van prostaatkanker (RR 1.63). Gedurende mediaan 56.8 maanden na diagnose bleek de prognose, afgemeten aan de biochemische progressie-vrije overleving, echter niet significant verschillend.

In **hoofdstuk 8** worden risicofactoren geidentificeerd van mannen bij wie ten tijde van diagnose geen metastasen konden worden aangetoond, maar bij wie zich later in het beloop

wel metastasen ontwikkelden. Van 1993 tot 1998 werd bij 633 mannen niet gemetastaseerde prostaatkanker gediagnosticeerd. Gedurende een follow-up van 7,5 jaar werd bij 41 van hen metastasen gevonden. De 10-jaars metastase-vrije overleving bedroeg 89,6%; de algemene overleving 64,7%. In een multivariabel model volgens Cox bleken 2logPSA, biopsie Gleason score en het aantal biopten met prostaatkanker per biopsie onafhankelijke voorspellers voor het ontwikkelen van prostaatkankermetastasen. Het aantal mannen met prostaatkanker die geen metastasen ontwikkelden was opmerkelijk hoog. Het is onduidelijk in hoeverre dit het gevolg is van de gunstige effecten van vroegopsporing en in hoeverre van de overdiagnose. De geidentificeerde prognostische factoren voor door vroegopsporing gevonden kankers zijn dezelfde als die voor klinisch gediagnosticeerde kankers.

De Gleason score is een van de meest belangrijke prognostische factoren voor prostaatkanker. Echter, door toedoen van vroegopsporing naar prostaatkanker en de resulterende beweging naar laaggradige, laag-stadium prostaatkankers heeft de Gleason score een gedeelte van haar kracht als voorspeller verloren. **Hoofdstuk 9** beschrijft een studie naar de predictieve waarde van de hoeveelheid hoog-gradige (Gleason patroon 4 en 5) prostaatkanker in het biopt op de PSA-terugkeer en op de klinische terugkomst van de ziekte. Het studiecohort bestond uit 281 mannen uit de ERSPC die een prostatectomie ondergingen. Na deze groep mediaan 7 jaar vervolgd te hebben, hadden 39, 24 en 12 mannen een PSA≥0,1 ng/mL, PSA≥1,0ng/mL en klinische ziekteterugkomst. In een multivariabel Cox model bleken PSA, lengte van de tumor en lengte van hooggradige tumor in de biopsie significante voorspellers te zijn van ziekteterugkeer. De Gleason score was hier geen significante voorspeller. De lengte van hooggradige kanker in het biopt bleek de belangrijkste voorspeller te zijn voor de terugkeer van prostaatkanker na een prostatectomie. We stellen dan ook voor dat, naast de Gleason score, ook de lengte van Gleason patroon 4/5 in het pathologie rapport vermeld zou moeten worden.

Daar de incidentie:mortaliteit ratio voor prostaatkanker sterk is toegenomen, is het belangrijk om kankers goed te kunnen classificeren naar risico. Een manier om dit te doen is het gebruik van nomogrammen. In **hoofdstuk 10** wordt een nomogram gebruikt om te berekenen hoeveel mannen uit het ERSPC cohort indolente ziekte hebben en op basis daarvan in aanmerking zouden komen voor het voeren van een afwachtend beleid. Het gebruikte nomogram werd afgeleid van het Kattan nomogram en is gevalideerd en ge-recalibreerd met behulp van de ERSPC data. Van 1.629 mannen bij wie in de eerste twee rondes prostaatkanker werd gevonden, kwamen 825 in aanmerking voor het gebruik van het nomogram. De overige mannen hadden ziekteparameters waarbij het onwaarschijnlijk was dat zij indolente ziekte zouden hebben. Van de 825 mannen hadden 485 (59%) berekende indolente ziekte. Dit is 30% van de totale groep mannen. Als kankers in de tweede ronde werden gevonden, dan was de kans op indolente ziekte groter dan bij eerste ronde kankers (44% vs 23%; P<.001). Dit nomogram kan in de toekomst gebruikt worden om te beoordelen of mannen in aanmerking komen voor een afwachtend beleid.

In het *vierde deel* van dit proefschrift wordt onderzoek gepubliceerd naar een manier om te zorgen dat de overdiagnose die het gevolg is van vroegopsporing niet overgaat in overbehandeling met de geassocieerde bijwerkingen. Ethische, medische en financiele argumenten zullen de urologische gemeenschap ertoe dwingen om bij iedere nieuwe prostaatkankerpatient te evalueren of het mogelijk is om bij de patient af te wachten met het behandelen. In **hoofdstuk 11** worden selectiecriteria voor zo'n afwachtend beleid toegepast op alle mannen die in de eerste ERSPC ronde gedetecteerd werden. Deze selectiecriteria waren: klinisch stadium T1C of T2; Gleason score 3+3 of minder; PSA dichtheid 0.2 of kleiner en een maximum PSA van 15 ng/mL. Van 1.014 mannen kwamen 293 (28.9%) hiervoor in aanmerking. Hun gemiddelde leeftijd bedroeg 65,7 jaar en de gemiddelde PSA waarde was 4,8 ng/mL. Van deze mannen die in principe in aanmerking gekomen waren voor het afwachtende beleid ondergingen in werkelijkheid 136 mannen een prostatectomie, 91 radiotherapie en bij 64 werd daadwerkelijk afgewacht. De follow-up was 80.8 maanden. De 8-jaar prostaatkanker-specifieke overleving was 99.2%; de algehele overleving 85.4%. Drie mannen overleden aan prostaatkanker; niet een uit de afwachtend beleid groep.

Als eenmaal de juiste mannen zijn geselecteerd bij wie afgewacht kan worden met behandelen, dan is vervolgens belangrijk om op het juiste moment bij de juiste mannen wel in te grijpen. PSA-kinetica spelen hierbij een belangrijke rol. **Hoofdstuk 12** beschrijft deze in een cohort van 278 mannen met door vroegopsporing gevonden prostaatkanker bij wie werd afgewacht met behandelen. Alle mannen hadden T1C/T2, PSA≤15 ng/mL, Gleason score≤3+3 prostaatkanker. De PSA verdubbelingstijd werd berekend in mannen met tenminste drie PSA-metingen (N=233). Van deze mannen had 44.2% een PSA verdubbelingstijd langer dan 10 jaar of een halveringstijd. Geconcludeerd kon worden dat er een belangrijke groep mannen is die zonder dat er ingegrepen wordt, stabiele ziekte hebben en dat er zelfs een aanzienlijke groep is bij wie het PSA daalt over de tijd.

Het *vijfde deel* van dit proefschrift geeft een literatuur overzicht en plaatst de onderzochte items in perspectief. Verder geeft het de wetenschappelijke basis weer voor de prosectieve studie die het resultaat is van dit proefschrift: de PRIAS studie (Prostate cancer Research International: Active Surveillance). Deze internationale studie wordt nader toegelicht in de epiloog van dit proefschrift. Wij zijn voornemens om richtlijnen te creeren die gebaseerd zijn op wetenschappelijk onderzoek. Verder is het ons doel om de overbehandeling van prostaatkanker zoveel mogelijk te beperken zonder daarmee de overlevingscijfers van deze ziekte nadelig te beinvloeden. Via deze weg proberen wij de nadelige effecten van vroegopsporing naar prostaatkanker te minimaliseren. We creeren een beslisprogramma voor behandelaars van prostaatkankerpatienten dat via internet beschikbaar is (www.prias-project.org). Daarmee limiteren we ook de kosten van de gezondheidszorg. Bovendien kan een database, een serumbank en een weefselbank worden opgebouwd, waarmee verder onderzoek gedaan kan worden. Tevens wordt een kwaliteit-van-leven studie geimplementeerd.

Curriculum Vitae

The author of this thesis was born on June 25th 1979 in the town Boxtel, the Netherlands. After graduating from college at the Dr. Moller College in Waalwijk, he studied medicine from 1997 to 2004 at the Erasmus University in Rotterdam. He published his first peer-reviewed paper during his senior-internship in General Surgery at the Reinier de Graaf Hospital in Delft.

On August 20th 2004 he graduated from medical school to become a medical doctor (M.D.). He then started working on this thesis as a PhD student in the European Randomized study of Screening for Prostate Cancer (ERSPC) research group of Professor F.H. Schröder.

The author started his residency to become a urologist at January 1st 2007 at the department of General Surgery of the Albert Schweitzer Hospital in Dordrecht (clinical supervisor: dr. R.J. Oostenbroek, General Surgeon). He will return to the Erasmus MC on January 1st 2009 for the urological continuance of his training (clinical supervisor: dr. G.H. Dohle, Urologist).

Dankwoord

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Op het moment dat ik dit schrijf kan ik me nog moeilijk voorstellen hoe het is om op een later moment dit boekje in mijn handen te hebben. Het schrijven van een proefschrift is voorwaar geen sinecure; het kost veel tijd en moeite. Momenten van euforie werden afgewisseld met tijden van relatieve somberte. Er zijn een aantal mensen die ik moet bedanken omdat ze een bijdrage hebben geleverd aan het huidige proefschrift of omdat ze zelfs een voorwaarde waren voor het ontstaan ervan.

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