POPULATION BASED SCREENING FOR PROSTATE CANCER: ASSESSMENT OF DIAGNOSTIC TOOLS AND CANCERS DETECTED.

Voor Car
Voor mijn ouders

POPULATION BASED SCREENING FOR PROSTATE CANCER: ASSESSMENT OF DIAGNOSTIC TOOLS AND CANCERS DETECTED.

BEVOLKINGS ONDERZOEK VOOR VROEGE OPSPORING VAN PROSTAAT KANKER: DIAGNOSTISCHE METHODEN EN GEDETECTEERDE TUMOREN.

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Taoïsme en winnen zonder strijd.

Volgens een oud verhaal vroeg een koning in het oude China eens aan zijn arts, afkomstig uit een geslacht van genezers, wie van hen het meest bedreven in de geneeskunde was. De arts die zo'n reputatie had dat zijn naam bijna synoniem geworden was aan de medische wetenschap in China, antwoordde: "Mijn oudste broer ziet de geest van de ziekte en verdrijft deze voordat zij vorm kan aannemen en daarom reikt zijn naam niet verder dan de voordeur van zijn huis. Mijn oudere broer smoort ziekten in de kiem en daarom is hij alleen maar in de buurt bekend. Zelf pas ik acupunctuur toe, schrijf ik geneesmiddelen voor en pas ik massage toe en daarom wordt mijn naam nog al eens genoemd en is hij ook bij koningen bekend".

Contents

List of abbreviations

ACT	α-1-antichymotrypsin
BPH	benign prostatic hyperplasia
DRE	digital rectal examination
ERSPC	European Randomized Study of Screening for Prostate Cancer
F/T ratio	free to total seum PSA ratio
PSA	prostate specific antigen
PSA-D	prostate specific antigen density (PSA / total prostate volume)
PSA-T	prostate specific antigen density of the transition zone (PSA / transition zone volume)
ROC curve	Receiver operating characteristics curve (sensitivity versus 1 minus specificity)
SEER	Surveillance, Epidemiology and End Results program (U.S.A.)
TRUS	transrectal ultrasonography

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Introduction and scope of the thesis

Over the past decade, considerable debate has occurred over the question whether or not to screen asymptomatic men for prostate cancer. It is unknown whether early detection and treatment of the disease will decrease the disease specific mortality. On theoretical grounds screening may prove to be successful. If the disease is diagnosed at an earlier stage of its development in which it is still organ-confined; treatment of the disease has a higher chance of being curative. Comparisons have been made [1, 2]with the effective strategy [3, 4] of breast cancer screening. Similar parallels however, can be drawn between prostate and lung cancer screening in which a shift towards earlier (potentially curable) stage did not reduce the disease specific mortality in screenees [5]. To conduct a randomized screening study with prostate cancer mortality as the major endpoint is one possible solution to the present controversy. For this purpose the European Randomized Study of Screening for Prostate Cancer (ERSPC) has been initiated [6]. The studies presented in this thesis are conducted within the Rotterdam section of the ERSPC to investigate the feasibility of screening and early detection of prostate cancer in the general population. Intermediate endpoints of the study are:

1. Assessment of the efficiency of the screening tests. Serum Prostate Specific Antigen (PSA) Digital Rectal Examination (DRE) and Transrectal Ultrasonography (TRUS).
2. To evaluate the morbidity related to the screening procedure.
3. To study tumor extent at the time of diagnosis.

The first part (Part A) of this thesis is therefore devoted to the diagnostic tools and their performance. The use of PSA, DRE and TRUS for the detection of localized prostate cancer is widespread but little is known about the performance of these tests in the general population. Is it possible to reduce the amount of false positive test results without compromising on the potential benefit on prostate cancer mortality? Are subgroups identifiable with an increased risk of having prostate cancer within the screened population?

In the second part (Part B) of this thesis the biopsy procedure is evaluated. What are the complications of the biopsy procedure? Are there identifiable riskfactors for complications after biopsy? To what extent and why are cancers missed by the systematic sextant biopsy procedure?

The final part of this thesis deals with the features of the tumors detected through population based screening. Is there a relationship between tumor characteristics and the outcome of the various screening tests? Does population based screening detect prostate cancer in an earlier stage of development?

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Chapter I

Screening for prostate cancer: More questions than answers*.

John B.W. Rietbergen and Fritz H. Schröder

Introduction

Whether prostate cancer screening should be applied to the male population or not, remains an extensively debated issue [1][2]. Reference can be made to the favorable results of breast cancer screening and the surprisingly unfavorable results of lung-cancer screening [3]. Since 1993 the American Urological Association (AUA) and the American Cancer Society (ACS) have recommend annual prostate specific antigen (PSA) testing and rectal examinations beginning at age 50 for early prostate cancer detection and at age 40 in men belonging to identifiable risk groups [4][5]. In most European countries, particularly in Northern Europe, routine application of screening procedures for prostate cancer is not accepted for a number of reasons: There is limited knowledge of the natural history of prostate cancer diagnosed at screening and the increasing gap between lifetime incidence and mortality suggests that there is a substantial risk of overdiagnosis and subsequent overtreatment. There is no reliable information on the effectiveness of treatment from randomized trials. The benefit of prostate cancer screening, in terms of reducing prostate cancer specific mortality, has not yet been shown. Adami and coworkers question whether even a randomized trial of screening for prostate cancer meets the ethical requirements [6]. In this chapter the issues that fuel the prostate cancer screening debate are reviewed.

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Is prostate cancer an important health problem

Incidence and mortality

The age and common co-morbidity of prostate cancer patients, coupled with an often slow rate of growth, have in the past resulted in widespread adoption of conservative policies of surveillance and palliative treatment rather than active treatment in many countries. However, incidence and mortality rates show the importance of the disease. The 1994 report of the Netherlands Cancer Registry shows an incidence of 6,315 cases in a male population of approximately 7.5 million. The crude rate is 83.0 cases per 100,000 person-years, the European standardized rate is 87.2 cases per 100,000 person-years. The mortality amounts to 2,374 men, the crude rate is 31.2 cases per 100,000 person-years, the European standardized rate is 34.1 per 100,000 person-years. Prostate cancer mainly occurs in men over 60 years of age; incidence and mortality rates are only 5.5% and 2.2%, respectively, between the age of 40 and 60 years, both rates rising steeply thereafter. Prostate cancer is the second most diagnosed cancer in males after lung cancer [7]. The prostate cancer incidence-rates are still rising whereas lung cancer incidence-rates are decreasing. The rise in incidence by far exceeds the modest rise in mortality.

Geographical patterns

The incidence of prostate cancer has risen dramatically over the past two decades, the United States ranking as having the highest incidence in the world. The effect of increasing male longevity and, above all, the increasing awareness and screening activities are responsible for this phenomenon. The increase in incidence is almost entirely due to the detection of localized disease, with no appreciable increase in metastastatic disease. The mortality rates remained relatively constant [8][9], Potosky et al. also state that the "epidemic of prostate cancer" is likely the result of the increasing detection of tumors as a result of increased prostate specific antigen (PSA) screening. Within Europe the highest incidence is recorded in Sweden and most Northern European countries, while the lowest incidence is found in the Mediterranean countries [10]. The increased incidence in Europe is not as marked as that in the U.S.A.; however, as a result of increasing male longevity alone, Boyle et al., expect an increase of 67% in prostate cancer incidence up to the year of 2020 in the European community [11]. Since public awareness and screening activities are likely to increase this may be a rather pessimistic view.

Lifetime risk

An alternative way to look at prostate cancer as a public health problem is to assess the cumulative risk or lifetime risk. In the Netherlands the cumulative risk of being diagnosed with prostate cancer between the age of 0 and 74 is 6.26 %. The cumulative risk of prostate cancer specific death between the age of 0 and 74 is 1.4% [7]. However, prostate cancer develops mainly in elderly men, thus it is useful to calculate the accumulation of risks over time for the subset at risk i.e. men of 50 years old and older, to observe the impact of the disease within this age group. Seidman and associates estimated the probability in 50-year-old white males of eventually developing prostate cancer at 9.5% using the SEER data relating to the period 1975 to 1980. The estimated risk of dying from prostate cancer was 2.9% [12]. A similar analysis for the incidence of prostate cancer was done in the 1994 report of the Netherlands cancer registry. The cumulative risk to be diagnosed with prostate cancer from the age of 55 until death is 9.9% [7].

Comment

These figures indicate that prostate cancer is a considerable public health problem. The fact that the population in most western countries is aging and the life expectancy is increasing will emphasize the importance of this disease. The epidemiological importance of a disease however, does not in itself provide justification for screening unless an important positive effect on mortality of early detection can be demonstrated.

Natural history

The natural course of prostate cancer is in some aspects poorly understood. Knowledge of the natural course of a given disease is a prerequisite for the application of screening as a public health policy [13]. Screening for any disease is unlikely to reduce disease specific mortality if most early, localized cancers that are detectable never progress within the life span of the host, and most aggressive cancers are already too advanced for curative treatment when detection is possible. On the other hand, screening may reduce mortality if most early, localized cancers that are detectable will eventually progress and the early detection of biologically aggressive cancers offers a window of opportunity during which detection and cure is possible.

Latent cancer

One of the unique properties of prostate cancer is the high prevalence of histological changes recognizable as cancer in surgical or in autopsy specimens and the much lower incidence of clinical disease. Prostate cancer is very often found at autopsy, the prevalence increases with age [14-17]. Such tumors are called "latent" carcinomas. In table 1 the results of four autopsy series are described. The differences in prevalence are probably the result of differences in preparative techniques, interval of sections, fixation and staining methods. The cumulative risk that a 50-year-old man will eventually have such a histological malignancy is approximately 30%.

Age	*Franks [14] (N=210)*	*Gaynor [15] (N=1050)*	*Holund [16] (N=173)*	*Saker [17] (N=152)*	*overall*
30-39	0%	4%	0%	27%	16/91=18%
40-49	0%	5%	12.5%	34%	24/198=12%
50-59	29%	10%	8.7%	-	38/302=13%
60-69	30%	18%	12.5%	-	41/163=25%
70-79	40%	28%	25.8%	-	119/400=30%
80-89	67%	39%	37.1%	-	61/145=42%
90^{+}	100%	40%	60%	-	7/12=58%

Table 1:

Percentage of men with latent prostate cancer at autopsy by age groups.

Unfortunately the characteristics in terms of grade of differentiation, tumor volume and stage were not described in these series.

More recently information about unsuspected prostate carcinoma has become available from prostate specimens removed at the time of cystoprostatectomy, performed for cancer or other pathologic conditions of the bladder [18-20]. These prostate cancers, not identifiable with digital rectal examination (DRE), are stated to be compatible with the autopsy cancers. The results of three such cystoprostatectomy series are described in table 2.

	Montie [18]	*Kabalin* [19]	*Ohori* [20]
Mean age (range)	62 (34-80)	64 (31-83)	-
Number of cystoprostatectomy specimens (normal DRE)	72	66	90
Number of cancers (%)	33 (46%)	25 (38%)	90 (-)
Gleason Score ≥ 6 (%)	12 (36%)	-	-
Gleason pattern ≥ 4 (%)	-	0 (0%)	10 (11%)
Mean tumor volume (ml.)	-	0.11	0.04
(Range)	-	(0.01-1.10)	(0.001-6.1)
Capsular penetration (%)	7 (21%)	0 (0%)	3 (3%)
Positive margins (%)	2 (6%)	0 (0%)	0 (0%)
Seminal vesicle invasion (%)	1 (3%)	0 (0%)	0 (0%)
Positive lymph nodes	0	0	0

Table 2:

Characteristics of prostate cancer found incidentally at cystoprostatectomy. All with normal findings on digital rectal examination (DRE).

These cystoprostatectomy series show a prevalence of approximately 40%, which indicates again that the prostate cancers that are clinically diagnosed form only the proverbial "tip of the iceberg". Stamey and coworkers [21] observed a similar prevalence in a series of 139 consecutively performed cystoprostatectomies. Fifty-three of the 55 men with prostate cancer had normal DRE findings. In this paper it is assumed that cancer progression is proportional to the tumor volume. The 1973-1977 SEER data [22] were used to calculate the lifetime probability at birth of a man having a diagnosis of

prostate cancer. This was estimated on 8% (Stage A disease was excluded from this evaluation). This figure was compatible with the observation that 8% of the 55 cases of prostate cancer were 0.5 ml or larger. This led to the conclusion that tumors smaller than 0.5 ml are probably clinically insignificant. Ohori and associates [20] compared their series of cystoprostatectomy cancers (in which the series of Stamey et al. were included) with a series of radical prostatectomy specimens performed for clinically detected prostate cancer. They concluded that unsuspected carcinoma found at autopsy or cystoprostatectomy is usually small, well or moderately differentiated and organ confined.

The natural course of clinically diagnosed prostate cancer

At the time of diagnosis, prostate cancer has often spread beyond the prostate. In the U.S.A. and in most European countries more than 40 % was not organ confined or metastatic in the pre screening era [23]. In the Netherlands the stage distribution of 4708 cases of prostate cancer diagnosed between the years 1989 and 1994 in the Amsterdam cancer registry region has recently been described. In table 3 the stage distribution is shown in total numbers and percentages. Twenty-four percent of these cancers had already metastasized at the time of diagnosis. Sixty percent of these tumors were clinically confined to the prostate [24].

Stage	*TX*	*T1*	*T2*	*T3*	*T4*	*total*
M0/MX	230	744	1846	566	183	3569
M0/MX(%)	4.9	15.8	39.2	12.0	3.9	75.8
M+	173	30	539	208	189	1139
M+ (%)	3.7	0.6	11.4	4.4	4.0	24.2

Table 3:

Stage distribution of 4708 cases of prostate cancer diagnosed between 1989 and 1995 in the Amsterdam region (Visser and Horenblas, NTvG 52, 1996 [24]).

Abbreviations:

M0=no metastases; MX=metastases unknown; M+=metastases; TX=Tumor stage unknown; T1=Diagnosis through transuretral resection of the prostate; T2=Tumor within the prostatic capsule; T3=Tumor with evidence of extracapsular growth; T4=Tumor with evidence of invasion of the bladderneck or pelvic diaphragm or pelvis.

Once prostate cancer has metastasized the prognosis is poor. Cure is impossible and median survival is in the range of 180 weeks in spite of endocrine treatment [25]. Series of untreated metastatic prostate cancer patients are old and probably unreliable but showed that two-thirds of patients died within 9 months after diagnosis. In 485 cases of untreated metastatic prostate cancer the average duration of the disease from the first symptoms to death was 31 months [26]. In the series of 701 cases described by Nesbit et al. the mean survival was 21 months after diagnosis (range <1-180 months). The prostate cancer specific mortality rate was 82% [27].

Deferred treatment series

Information concerning the natural course of clinically diagnosed prostate cancer is available from several series of patients who were treated conservatively with observation and delayed hormonal therapy.

Handley et al. reported a series of 278 patients that were diagnosed with prostate cancer in the period between January 1978 and December 1985. They received no further treatment after the diagnosis until symptomatic progression occurred. Ninety-five percent of patients were diagnosed by trans-urethral resection of the prostate. Metastases were present in 19.4% of patients. The disease was considered clinically localized in 75% of cases. Nevertheless, only 30% survived 5 years compared with the expected survival rate of 65% for an age matched population. Prostate cancer was the cause of death cited in 42% of all patients at 5 years. The survival rate for well-differentiated prostate cancer was no different from that of an age matched population [28].

Johansson and coworkers are the authors of a paper with the title: High 10-year survival rate in patients with early, untreated prostatic cancer. A subset of 223 patients with localized prostate cancer was selected from a cohort of 654 men with prostate cancer. The grade distribution showed 66% well differentiated tumors, 30% grade 2 and 4% grade 3 tumors. The mean age was 72 years. During the mean observation period of 123 months (range 81-165 months) 34% showed progression, 56% died, but prostate cancer was considered the cause of death in 8.5% of these 223 men [29]. In a later report with a mean observation of 12.5 years prostate cancer was considered the cause of death in 10% of the original 223 patients [30].

In their most recent report the observations concerning the total cohort of 648 consecutive cases of prostate cancer with an average observation time of 168 months

(range 126-210 months) are described. At the end of the observation period 84% of patients in the original cohort had died. Thirty-seven percent of the deceased men were considered to have died from prostate cancer. In an additional 7% prostate cancer was considered a contributory cause. Of the initial 159 (25%) patients with metastasized disease 78% died from their disease, in an additional 6% their disease was considered contributory. The corrected 15-year survival rate was 71.8% among patients without distant metastases detected at diagnosis and 5.7% among those with metastases. In the initially untreated group of 223 men the prostate cancer specific mortality was 11% [31]. The series of Johansson, together with five other series were included in a pooled analysis by Chodak et al [32]. Actuarial survival statistics showed that grade is the most important parameter in predicting survival. The mortality due to prostate cancer among men with grade 1 and 2 disease was 13% at 10 years versus 66% in men with grade 3 disease. Ten years after diagnosis metastases had occurred in 19% (grade 1), 41% (grade 2) and 74% (grade 3) of cases.

The overall favorable result of conservative management within these series however, gives too optimistic a view of the reality. These series have been criticized severely for selection bias. This can be illustrated through comparison of the grade distribution within this pooled analysis and the grade distribution in other series of clinically diagnosed prostate cancer. The grade distribution shows 59% grade 1 tumors, 32% grade 2 tumors and 8% grade 3 tumors. The grade distribution in the general population registry of the previously described Amsterdam region shows 25% grade 1 tumors, 36% grade 2 tumors and 32% grade 3 tumors [24]. For T1 tumors the difference in grade between the two series is not very outspoken, both series show 57% of well differentiated tumors. Stage T2 tumors however, are well differentiated in 52% of cases in the series of Chodak versus 28% of cases in the Amsterdam series. Poorly differentiated tumors are seen in 6% of cases whereas 25% is seen in the Amsterdam region. Further criticism came from Aus and co-workers. These authors indicated that age was not evaluated as a risk factor with respect to the endpoints. The average age of 70 in the series of Chodak is high. This group concluded that low cause-specific mortality rates at 10 years of follow-up in series on deferred treatment comprising older patients with high competing mortality could not be extrapolated to younger patients with a low competing mortality [33].

In order to estimate the long-term survival of men aged 65 to 75 years old (mean 70.9) with conservatively treated newly diagnosed localized prostate cancer (between 1971 and 1976), Albertsen et al. recently conducted a study in such a way that biases observed in

the series by Chodak and Johansson were minimized. The collected data was population based and the original pathologic specimens were reviewed. The original hospital charts were reviewed in order to obtain a consistent score for patient comorbidities. Two important findings were demonstrated for this cohort: (1) Tumor histologic features are highly predictive of survival and (2) patient comorbidities are nearly as potent a predictor of survival as tumor histologic findings. Men having low grade (Gleason score 2-4) prostate cancer and aged 65 to 75 years face no apparent loss in life expectancy compared with an age matched general population [34]. This favorable outcome may be due to the natural history of the tumor or of the host. Moreover, since the health condition of the host has a significant impact on survival, a selection of healthier men with longer life expectancy than average may benefit from early detection and treatment.

Comment

One of the most important issues in the prostate cancer screening dilemma is the fact that many cancers for various reasons will never be a threat to the hosts wellbeing within his life span. If prostate cancer screening detects unimportant cancers this will lead to treatment of men for whom it is not necessary. The series described above however, indicate that prostate cancer is a progressive and potentially lethal disease when managed conservatively. Two factors appear to be decisive in the question whether prostate cancer is able to kill the host. (1) The biologic activity which is represented by the grade of the tumor. Poorly differentiated tumors metastasize within a short period of time and are generally lethal. (2) The time during which the tumor can progress is determined by the comorbidity and the age of diagnosis. It is still under discussion which factors are responsible for the intrinsic biologic activity i.e. why some tumors become aggressive and others remain latent. This can also be observed from the doubling time of prostate cancer, which shows that 79% of all patients have a doubling time of more than 24 months. Doubling times were faster in patients with higher stages and grades. This also implies that high volume tumors are generally more dangerous than small tumors [35, 36].

Are latent cancers and clinical cancers indistinguishable? According to some authors this is not the case. Ohori and Scardino showed that clinically detected adenocarcinoma of the prostate differs from that found incidentally at autopsy in important pathological features, such as volume, grade and extent. [20, 37, 38]

A series of papers from Stanford University show that the biological aggressiveness of

the cancer is directly related to tumor volume and histologic grade [39, 40]. Small, well-differentiated prostate cancer will not pose a threat to the host. However, determination with the current diagnostic tests of which lesions, that are still confined to the prostate, will progress and therefore require active treatment, and which will remain slow growing or inert, is a debated issue and will be addressed within this paper.

Primary prevention

Miniscule focuses of prostate cancer are already present in young adult men [17]. The prevalence of focal cancers found at autopsy varies little among different countries and races [41] whereas the incidence of clinical disease shows a considerable variation. These findings suggest that environmental and genetic factors may promote the occurrence of life-threatening prostate cancer. This hypothesis is enforced by the observation that the mortality of prostate cancer in Japanese migrants increases to half that of the indigenous population within two generations [42].
In a cohort of approximately 14,000 men dietary and lifestyle characteristics were evaluated in relation to subsequent prostatic cancer risk. Increasing consumption of beans, lentils and peas, tomatoes, raisin, dates, and other dried fruit were all associated with significantly decreased prostate cancer risk [43-45]. A high-fat diet is associated with a high risk because of increased androgen activity [46-48]. Genetic factors are related to the rare but clinically significant occurrence of prostate cancer in familial cases [49-50].

Comment
Further identification of environmental and genetic factors that influence the prostate cancer incidence will take time. A variety of agents are being evaluated in vitro and in vivo but it is not expected that results will be available at short notice [51-54]. The question whether dietary measures or the use of chemo-preventive agents can prevent prostate cancer will have to be tested in large randomized trials. Treatment of prostate cancer has adverse effects. The primary prevention of prostate cancer appeals to many struggling with the treatment of the disease. However, effectiveness costs, side effects, duration of the preventive treatment and difficulties in implementation will have to be studied first. Primary prevention trials and randomized trials of screening for prostate cancer have been initiated. It is unknown whether any of these approaches will reduce prostate cancer morbidity and mortality.

Secondary prevention-Rationale for screening

The series described by Nesbit and Bumpus [26,27] show that if prostate cancer is diagnosed when symptoms are present and left untreated, almost all men die from the disease. Curative treatment of prostate cancer is impossible once the disease has spread beyond the prostate [55]. At this time 40% of newly diagnosed cases are not localized when diagnosed. In a large series of men treated with radical prostatectomy for clinically localized prostate cancer, over 50% had pathological evidence of extracapsular disease and 23% had positive margins [56]. These patients are at risk for progression. Patients treated with radiotherapy have also shown significant rates of both biochemical and clinical progression [57]. Through the application of early detection regimes, if they are effective, cancer will be diagnosed at an earlier stage in its biological development.

Feasibility of early detection

It has been shown that early detection of prostate cancer is possible. The identification of PSA as a diagnostic tool has been a major contribution to the diagnostic arsenal [58]. Catalona et al. reported on 10,251 men aged 50 years and older without a history of prostate cancer who were initially screened with a serum PSA level. Men with a PSA level of 4 ng./ml. or higher underwent both digital rectal examination (DRE) and trans-rectal ultra-sonography (TRUS). A biopsy was performed if either of these procedures revealed abnormal or suspicious findings. This group was compared to a group of 266 concurrently studied patients who were referred for TRUS and biopsy because of an abnormal DRE. Sixty-three percent of 244 patients whose cancers were detected on initial PSA based screening had pathologically localized disease versus 43% of the 47 patients in the comparison group. Four men (1.6%) had positive bone scan and bone biopsy. Fifteen men (6.1%) had lymphnode metastases. [59]. In a more recent report 6,630 men were screened through determination of serum PSA and a DRE. In 1,167 biopsied men, 264 cases of prostate cancer were detected. Only three of these patients were found to have advanced disease. Of the remaining 261 patients, 162 were treated by radical prostatectomy. Seventy-one percent of these men had organ confined cancer [60]. Mettlin and associates reported on the 164 cases of prostate cancer detected in a cohort of 2,999 participants of the American Cancer Society-National Prostate Cancer Detection Project. These men were screened through PSA, DRE and TRUS. One hundred and

three men were treated by radical prostatectomy. Sixty-two percent of cancers were pathologically confined to the prostate [61].

Comment

The results of these casefinding studies show that early detection is possible. There is a shift towards the detection of earlier stage prostate cancer with any form of PSA based screening. The percentage of metastasized cancer is significantly lower when compared to series of prostate cancers not detected through screening. This stage reduction however, does not provide evidence that prostate cancer screening will decrease prostate cancer mortality. Two biases are associated with screening: Bias as a result of increased survival in the screened group due to detecting the tumor earlier without genuinely prolonging life (lead time bias) and bias due to detecting slower growing tumors, that would never have led to mortality due to prostate cancer, in the screened men (length time bias). A randomized controlled trial with prostate cancer mortality, as endpoint is needed to avoid these biases. Not only would this avoid selection bias, but also by using reduction of prostate cancer specific mortality as the measure of outcome rather than survival after diagnosis, lead and length time bias can be avoided. One study estimated that the lead-time will average 5.5 years [62]. In a nested case control study of men without comorbidity providing plasma samples before a ten year follow-up the baseline PSA level could have moved forward the diagnosis of prostate cancer by an average of 5.5 years. Lead-time distributions for aggressive and non-aggressive tumors were the same.

Diagnosis of prostate cancer-Screening tests and their performance

Three methods in various combinations are commonly used in the early detection of prostate cancer. Palpation of the prostate through digital rectal examination (DRE) is the traditional method. In 1967 an additional diagnostic tool became available: Trans-rectal ultrasonotomography of the prostate (TRUS) [63]. This was the first method to actually visualize the prostate itself. Criteria for recognition of prostate cancer were defined in the following years [64]. The identification of Prostate Specific Antigen (PSA) has added to the methods available for early detection of prostate cancer [65].

Prostate Specific Antigen

PSA is a 34 K Dalton serine protease, which can be detected in semen and male serum [66]. It is part of the human kallikrein family. The production takes place in the epithelial cells of the prostate, also in adenomatous and prostate cancer tissue [67]. Recently other PSA producing sources such as pancreas and salivary glands in both men and women have been identified [68, 69]. It is unclear whether this will have clinical consequences in the near future. In the daily practice however, PSA is still regarded as prostate specific. PSA is most probably metabolized in the liver [70].

PSA is not tumor specific; several benign conditions may increase the serum PSA concentration. Benign prostate hyperplasia is the most common cause of elevated PSA levels. Aus and coworkers showed that after trans-urethral resection of the prostate with a benign histopathologic specimen, PSA should be expected to be within the normal range [71]. Prostatic needle biopsy, prostatic massage, trans-rectal ultrasonography [72] and digital rectal examination [73] may all lead to an increase of serum PSA. It is likely that ejaculation leads to a transient increase of serum PSA [74,75] however, unchanged level [76, 77] and decrease [78] have been described as well. The consequence is that bloodsamples should be taken prior to any examination of the prostate.

PSA in nested case control studies

Serum PSA rises slowly with age and increasing prostatic volume. The average increase is small (0.3 ng./ml. per gram of tissue) [79] in comparison with the 3.5 ng./ml. per gram of malignant tissue [80]. The concept of the more pronounced PSA increase in prostate cancer was evaluated retrospectively in four nested case control studies [62,81-83]. In large groups of men, bloodsamples were drawn and stored for many years. This allowed

comparison of PSA values in those who developed clinically evident prostate cancer and those that did not. The advantage of this method is that no assumptions will have to be made for clinical relevance of the detected cancers. The results however, are fully dependent on the reliability of the data provided by the cancer registry. In the study by Gann and coworkers [62], a single PSA determination at a cutoff level of 4 ng./ml. would have detected nearly 80% of all aggressive cancers within 5 years and about 50% appearing 9 or 10 years later. Only 96 of 1098 men who were not diagnosed with prostate cancer had a false positive test result. Optimal validity was achieved at a PSA cutoff of 3.3 ng./ml.. Whittemore et al. calculated the sensitivity and specificity for a PSA cutoff level of 4 ng./ml. and for clinical cancer being diagnosed within 7 years. In men younger than 65 years the sensitivity was 65%, the specificity was 94%. In men of 65 years and older the sensitivity was 100% and the specificity was 70%.
All studies agree that PSA determination is a suitable test for early detection of prostate carcinoma.

PSA threshold value

In the early studies of prostate cancer detection a cutoff value of 4.0 ng./ml. was arbitrarily chosen as the upper limit of normal [58]. This PSA cutoff is mainly used to limit the number of men that undergo the more laborious screeningtests as DRE and TRUS. In a later study biopsies were performed if the PSA level was above 4 ng./ml. or DRE was suspicious for cancer [84]. Receiver operating characteristic (ROC) curve analysis showed the 4 ng./ml. cutoff value to be optimal. A similar analysis performed earlier by Labrie and associates showed optimal sensitivity and specificity (respectively 81% and 85%) using a PSA threshold of 3 ng./ml., using the same PSA assay [85]. It should be noted that the description of the performance of tests in prostate cancer screening through sensitivity, specificity and positive predictive value is hampered by the fact that the denominator is not known. Instead of the true prevalence of prostate cancer within the population under study the number of positive biopsy results is used.

PSA in screening

The increasing chance of detecting prostate cancer with increasing PSA levels has been demonstrated repeatedly in case finding studies and population based screening projects. Generally 70% to 80% of all cancers are detected in the PSA range above 4 ng./ml., in approximately 10% to 17% of the population under study [60,86-89]. At normal PSA

values DRE and in some cases TRUS are responsible for the detected cancers. Crawford and coworkers [90] described the detection of prostate cancer in 31,953 eligible subjects screened in centers throughout the U.S.A.. Among 1307 subjects who underwent biopsy, 322 cases of prostate cancer were detected. The cancer detection rate for PSA was 3.6% and for DRE 3.0%. This percentage was 4.7% if both tests were positive. The positive predictive value for elevated PSA levels was 31.6%. For DRE this was significantly lower with 25.5%. Thirty-one percent of cancers were missed by DRE and diagnosed through PSA only. DRE detected 27.6% of cancers that would have been missed by PSA. Again the description of the properties of PSA as a screening test is difficult since not all men in the population under study are biopsied. The true number of prostate cancer cases remains unknown. It must be assumed that impalpable and invisible cancers are also present at PSA levels below a cutoff of 4 ng./ml.. This implies that the positive predictive values, sensitivity and specificity values reported in literature are incomparable and incorrect. These values are dependent on the screening tests used, the biopsy indications and the biopsy technique in use. If TRUS would have been used or more biopsies had been taken in the latter study it is likely that more cases of cancer would have been detected at PSA levels below 4 ng./ml.. This would have altered the described values.

The most important observation however, is the fact that PSA is the strongest predictor for prostate cancer and that DRE is of limited additional value.

The use of PSA and DRE in a screening setting will detect prostate cancer in approximately 4% of subjects [60,86,89] in the age group of 55 to 75. This is only true for population based screening programs. In a clinic population of symptomatic urological patients detection rates up to 14.6% have been described [91]. This shows that the detection is strongly population dependent.

DRE

DRE has been used for the detection of prostate cancer in several large series. Chodak et al. used DRE as the only test in the screening of 1,672 men aged 51-70 years. A detection rate of 1.4% was found [92]. Although 68% of these cancers were clinically localized, 50% of these patients showed capsular penetration after examination of the radical prostatectomy specimen. It was concluded that DRE detects prostate cancer relatively late. Pedersen et al. [93] diagnosed 13 cases of prostate cancer in 1163 screened men (1.1%). Both a urologist and a general practitioner did the examinations. The positive

predictive value within this population was 29%, 35% for the urologists and 27% for the general practitioner. This illustrates the dependence of DRE on experience and quality of performance. Smith and Catalona also showed a considerable inter-examiner variability. The agreement among urologists was only fair. The interexaminer variability was greater between faculty and resident examiners showing that experience plays an important role in DRE [94]. However, in spite its shortcomings, DRE increases significantly the detection rate that can be achieved with PSA alone.

TRUS

Prostate cancer can be visualized by TRUS as a hypo-echoic structure within the peripheral zone of the prostate [95]. However, not all hypo-echoic lesions prove to be prostate cancer and not all cases of prostate cancer appear to be hypo-echoic. Terris et al. examined 51 patients with normal DRE findings by TRUS before they underwent radical cystoprostatectomy for transitional carcinoma of the bladder. The ultrasound findings were compared to the pathological slides. In 8 patients a hypo-echoic lesion proved to be cancer. Nine patients had abnormal TRUS findings but no cancer. Seven patients with normal TRUS findings had prostate cancer. Based on these results the positive predictive value is 47%, the sensitivity is 53% and the specificity is 75% [96]. Lee and co-workers biopsied 256 patients with a hypoechoic lesion and detected 104 cancers. The positive predictive value of 41% decreased to 24% if DRE was normal, and to 12% if PSA was below 4 ng./ml.. TRUS alone had a positive predictive value of 5% [97]. This is in line with the observations within the American Cancer Society National Prostate Cancer Detection Project. In this study the positive predictive value of TRUS at PSA levels above 4 ng./ml. is significantly higher (33%) than that of DRE (27%). Under a PSA level of 4 ng./ml. the positive predictive value of DRE and TRUS are similarly low (respectively 6.4% versus 5.4%) [86]. This shows that if DRE and TRUS are used for the detection of prostate cancer at PSA levels below 4 ng./ml. the additional value is limited. This is also confirmed by the receiver operator characteristic curve analysis by Ellis et al.. PSA, DRE and TRUS were evaluated in 1,001 six-sector prostate needle biopsies. This analysis showed that PSA is the best predictor for prostate cancer with an area under the curve of 0.64. The areas for DRE and TRUS were 0.58 and 0.50 respectively [98]. Again the additional value of DRE and TRUS under a PSA level of 4 ng./ml. was limited. DRE or TRUS alone each detected 5 cancers of the total 253 cases at the cost of 133 additional biopsies (13.3% of all biopsies performed).

The role of TRUS in screening for prostate cancer is more controversial than the use of DRE. In accordance with DRE it is a strongly investigator-dependent technique but above all it is relatively expensive and time consuming. Undisputed however, is the value of TRUS for the visualization of the prostate and in guiding the biopsy needle in the case of systematic sextant biopsies.

Stage T1C prostate cancer

Through the combined use of PSA, DRE and TRUS in the diagnostic procedure for detection of prostate cancer it became clear that some cases of prostate cancer are neither visible, nor palpable and were identified by needle biopsy. This has led to a new category in the TNM classification of prostate cancer: Stage T1C i.e. tumor identified by needle biopsy [99]. From the previously described autopsy series it became clear that 30% of men over 50 years of age harbor malignant cells within their prostates. Only a small subset of these cancers form a threat to their host. One of the first questions that rose was whether T1C tumors are different from incidental tumors found at autopsy? Several authors have reported on the characteristics of T1C prostate cancer. Epstein et al. described a case series of 157 consecutive men who underwent radical prostatectomy for clinical stage T1C disease. Sixteen percent of tumors were considered as insignificant and 10% as minimal lesions, based on tumor volume and grade [100]. Stage T1C tumors more closely resemble stage T2 cancers than they do incidental prostate cancers detected at cystoprostatectomy. Their volume is about 50 times greater [20,101,102]. One difference between T2 and T1C cancers was the gland size. The prostates harboring T1C cancers were significantly larger, which might explain the impalpability [103].

Improvement of the specificity of PSA based screening: Reducing the number of biopsied men

A high PSA level, abnormal findings on DRE and/or TRUS increase the chance of diagnosing prostate cancer in a screened man. At low or intermediate PSA levels the false positive rate is high, which results in a high amount of unnecessary biopsies. The use of DRE and TRUS will reduce the number of unnecessary biopsies however, stage T1C prostate cancers that are not visible by TRUS or impalpable will be missed. T1C cancers form a potentially curable subset that amounts to 25 to 40% of all cancers diagnosed within most screening programs.

Prostate Specific Antigen-Density (PSA-D)

PSA as a screening test identifies more cases of prostate cancer than DRE and/ or TRUS. A complicating factor in PSA based screening is the fact that elevated PSA levels are caused by both benign prostate hyperplasia and prostate cancer. PSA alone is unable to discriminate between these conditions. The finding that PSA levels are proportional to the volume of benign prostate tissue and the volume of the cancer present [79] has led to the assessment of PSA corrected for total prostate volume in an attempt to avoid unnecessary biopsies. Babaian et al. found the suspicion for the presence of cancer to be greater if the volume of the prostate measured through TRUS is smaller than 25cc at elevated PSA levels [104, 105]. The results of Benson and co-workers suggest that the quotient of PSA and the prostate volume may be useful in distinguishing prostate cancer and BPH [106, 107]. A ROC curve analysis for PSA-D in a prospective evaluation suggested that the best cutoff point for biopsies was a PSA-D value of 0.15 ng./ml./cc. Thus suggesting that the normal prostate volume at a PSA level of 4 ng./ml. is 26-cc [108], which is in line with the findings of Babaian et al.. Littrup et al. concluded that PSA-D was superior to other tests and test combinations, a 16-55% reduction of biopsies could be achieved with a respective loss of otherwise diagnosed cancers of 4-25% [109]. Although there is some optimism, several authors have reported that the use of PSA-D at a cut-off level of 0.15 results in half of the tumors being missed and that biopsies should be indicated by PSA rather than by PSA-D [110-112]. Loss of cancers detected not only depends on PSA-D threshold value but also on the characteristics of the population. A ROC curve analysis by Ohori and associates showed a higher specificity for PSA-D but only in a small subset of patients, those with a PSA value >10 ng./ml. and PSA-D below 0.15 [113]. Similar findings were obtained by Brawer et al [114]. The use of PSA-D will improve the specificity at the cost of loss in cancer detection. It may prove to be useful in well-defined subsets of screened men. One of the major disadvantages of the use of PSA-D is that the prostate volume has to be measured by trans-rectal ultrasound, which is time-consuming, and expensive.

Age specific reference ranges

PSA not only rises slowly with prostate volume, but also with age [115, 116]. In order to make PSA a more discriminating tumor marker for detecting significant cancers in older men and to find more potentially curable cancers in younger men Oesterling et al suggest the use of four different PSA threshold values, 2.5 ng./ml.; 3.5 ng./ml.; 4.5 ng./ml. and

6.5 ng./ml. in men in the fourth, fifth, sixth and seventh decade respectively. The use of these ranges in men aged 60 years and older saved 5.5% of biopsies at the cost of 0.6% of cancers detected [117]. The hospital records of 4,579 patients with stage T1C, T2 or T3A prostate cancer who underwent radical prostatectomy were reviewed. Subsequent simulation of age specific reference ranges, showed an increase in detection of 18% in younger men and a decrease in detection of 22% in the older men. Ninety-five percent of missed cancers would have favorable pathological findings [118]. El-Galley et al. concluded that the use of age adjusted PSA is the most valuable for patients over the age of 70, of whom 22% would be spared TRUS with biopsy [119]. Catalona et al. however found that the number of biopsies performed for the detection of one case of prostate cancer remains constant over the age groups suggesting that the use of age specific reference ranges does not enhance the specificity [84]. Furthermore, application of age specific reference ranges in men 50 to 59 years old would have resulted in a 45% increase of biopsy indications and a projected increase of 15% in cancer detection. In the sixth and seventh decade the increased PSA threshold level would save respective 15% and 44% of biopsies at the cost of respective 8% and 47% of organ confined tumors. This study concludes that the use of PSA at a cut-off level of 4 ng./ml. is preferable.

Ratio of free and total prostate specific antigen (free/total ratio)

A major part of PSA in serum of prostate cancer patients occurs as a complex between PSA and α_1-antichymotrypsin (ACT). Patients with prostate cancer have a significantly higher proportion of complexed PSA (PSA-ACT) than those with benign prostate hyperplasia [120]. Thus, men with a relatively high free PSA are more likely to have benign disease. The ability of the free to total ratio to discriminate prostate cancer and benign prostate hyperplasia was demonstrated in a retrospective non-randomized analysis [121]. This concerned well-defined cases of BPH: Men having a prostate volume of at least 40cc and negative biopsies and men with biopsy proven prostate cancer and normal gland volumes. The conclusion was that measurement of the percentage of free PSA improves the specificity of prostate cancer screening in selected men. This has repeatedly been confirmed in similarly designed studies. The results described in the paper of van Cangh and associates [122] are in line with these observations however, they also point out that the use of the free/total ratio in screening appears problematic due to the low prevalence of prostate cancer. In fact, within the Rotterdam section of the European Randomized study of Screening for Prostate Cancer (ERSPC), the discriminating ability

of the free/total PSA ratio, at a cut off value of 0.20, did only lead to a small improvement of area under the receiver operating characteristics curve which, due to large numbers, was statistically significant [123]. The use of a free/total ratio of 0.18 in addition to the PSA cut-off in the Göteborg (Sweden) site of the ERSPC would save 42% of biopsies at the cost of 12% of cancers detected (all men were biopsied if PSA was greater than 3 ng./ml.). When compared to a PSA cut-off level of 4 ng./ml. both sensitivity and specificity improved by the use of a free/total ratio of 0.18 [124]. In a subsequent study by Bangma et al. similar results were obtained in the PSA range between 4 and 10 ng./ml.. The use of a free/total ratio of 0.20 or less in combination with DRE would reduce the number of biopsies by 38% with 12% of carcinomas remaining undetected. However, the combination of DRE and PSA-Density value of 0.12 or more shows an identical performance [125]. A major advantage of the use of the free/total ratio above PSA-D lies in avoiding the use of trans-rectal ultrasonography. Various cut-off levels for the free/total ratio have been suggested, varying between 0.15 and 0.21 [126], however, cut-off values for clinical practice have not yet been established. It will be crucial if sensitivity is sacrificed, to understand what the contribution of undetected tumors to the desired decrease of prostate cancer mortality might be.

Comment

The reduction of negative effects of false positive indications for prostate biopsies leads inevitably to a decrease in prostate cancer detection. Knowledge of the cancers not detected is limited, i.e. although these cancers are often locally confined it is unknown whether they would be potentially lethal and not detecting these cancers would narrow the window of opportunity within a screening program. The use of age specific reference ranges seems to have little impact on the number of false negative biopsy indications and cancer detection but merely shifts the detection towards a younger age group. Since the value of mass-screening for prostate cancer is unknown, it is questionable whether this shift will improve the overall outcome of screening.

PSA-Density and the use of the free/total ratio of serum PSA will reduce the number of false positive biopsy indications. Cut-off values will have to be further evaluated. The major advantage of the use of the free/total ratio lies in the reduction of the workload by omitting TRUS.

TRUS guided systematic sextant biopsy

The use of TRUS with the possibility of taking multiple trans-rectal core biopsies of the prostate using fast spring loaded biopsy devices has become the standard procedure in the diagnosis of prostate cancer. The procedure is relatively safe and can be performed in an outpatient setting without the use of anesthesia. Minor adverse effects that are often reported are transient hematospermia and hematuria. Infection is a less innocent complication and may lead to septicemia and even death [127, 128]. Fortunately these complications are rare. Septicemia occurs in 0.3 to 3.5% of cases [129, 130]. Mortality has only been described in case reports.

The data derived from the autopsy series and cystoprostatectomy series show that the pool of prostate cancers is very large. The minority of these cancers is thought to be a potential threat to the host.

One of the concerns in early detection of prostate cancer is the sensitivity of the biopsy procedure. Terris et al. introduced the concept of systematic sextant biopsy [131]. Of the 442 cancers detected in 816 patients only 10% had a tumorvolume less than 0.5 cc and were thus considered insignificant. In a series of T1C cancers the percentage of insignificant cases was 16% [100] indicating that although insignificant cases are detected, the majority are considered large enough to be potentially dangerous (provided the parameters in use are reliable).

Not detecting potentially dangerous cancers is also undesirable. Daneshgari et al. calculated the probability of detecting low volume cancer with a total aggregate volume of 0.034 to 5.1cc. They found that the size of the prostate as well as the size and distribution of the lesions within the gland determine the chance of diagnosis by sextant biopsy. The chance of missing tumor was 27%. Furthermore a needle angle of 30° gave significantly better results than 45° or 60°. Sextant biopsies were superior to random biopsies [132].

In a retrospective series of 123 men a second sextant biopsy procedure within 6 months revealed 28 additional (23%) cases of prostate cancer. Ten of these cases were found in 66 re-biopsied men in the PSA range between 4-10 ng./ml. [133]. The accuracy of diagnosis may not only be related to the tumor volume but also to the gland volume in which the tumor resides. The positive-predictive values for a positive biopsy of PSA greater than 4 ng./ml. was reduced from 54% to 14% when gland volume increased from less than 20cc to greater than 100cc [134]. Uzzo et al. showed similar findings in a

multivariate analysis that patients diagnosed with cancer had significantly smaller prostates [135].

To improve the detection rate by biopsy and to reduce the sampling error Eskew, Bare and McCullough [136] increased the number of biopsies according to the prostate volume measured by TRUS. Thirteen to eighteen biopsies in a 5-region pattern are taken. The detection increased with 35% using this concept. No significant difference was found in tumor volume or Gleason score between the tumors found with the systematic sextant biopsy pattern and those detected in the additional series of biopsies. However, it should be noted that these figures come from a small series that needs further confirmation.

Prediction of stage, grade and insignificant disease

Several parameters are considered important in the prognosis of prostate cancer. Large tumor volume, high grade of malignancy and extracapsular extension are associated with a poor prognosis. Since prostate cancer screening detects prostate cancer in more men than are likely to experience disease progression it would decrease the uncertainty if the stage, grade and extent of the tumor would be known before the choice of treatment. Cases have been reported in which radical prostatectomy had been performed for biopsy proven cancer and after examining the specimen no cancer was found [137].

Prediction of insignificant disease

Terris et al. [131] treated 17 patients with less than 3mm of well differentiated cancer in one of six biopsies by radical prostatectomy. The tumorvolumes of these patients ranged from 0.04 to 10.1 cc. Eleven of these seventeen patients (65%) had volumes less than 0.5 cc. This ratio however, was reduced to 10% by taking a second set of sextant biopsies. Ravery et al. stressed the fact that a single positive biopsy in six does not predict a low-volume prostate cancer on an individual basis [138]. Twenty-four radical prostatectomies were performed for prostate cancer detected with one positive biopsy out of six. Capsular penetration was present in 29% and seminal vesicle invasion in 8%. If less than 10% of the biopsy core length was invaded by tumor all were free of extracapsular involvement. If the whole biopsy length was involved all patients had extracapsular cancer. The volume of cancer in the biopsy specimen, as a predictor for the volume of cancer in the radical prostatectomy specimen, was evaluated by Cupp and co-workers [139]. Regression analysis revealed a direct correlation. However, of 13 patients with 5%

or less cancer only 1 had a tumor volume less than 0.5 cc. They concluded that the biopsy specimen does not provide enough information for decisions on an individual basis. According to Epstein et al. insignificant tumor is predicted with 73% accuracy by a PSA- Density of less than 0.1 and no adverse pathological finding on needle biopsy or a PSA-D of 0.1 to 0.15 with less than 3 mm low to intermediate grade cancer in only one needle biopsy core [140].

Prediction of grade

When the grade of the biopsy specimen is compared to the radical prostatectomy specimen, undergrading is common [141, 142]. Possible explanations are: (1) The tendency to undergrade limited amounts of Gleason pattern 3 or 4 on needle biopsy. (2) The sampled nodule is correctly staged but multifocal higher-grade tumor is present elsewhere. (3) Heterogeneity of the grade within the tumor nodule induces sampling error [143]. The ability to predict tumor grade can be enhanced by considering the PSA value and PSA density [144]. Still poorly differentiated prostate cancer is only identified on biopsy in about 50% of cases [145].

Prediction of stage

The clinical stage is a poor predictor for the stage at radical prostatectomy [56]. Capsular penetration and seminal vesicle invasion can to some extent be predicted by the preoperative serum PSA concentration, Gleason patterns and the percentage of cancer in the biopsy specimen [146]. D'Amico and co-workers used the calculated prostate cancer volume to predict capsular penetration in clinically localized disease [147]. PSA, prostate volume and Gleason score are the parameters used. The formula was the result of a logistic regression multivariate analysis on 104 radical prostatectomy specimens.
Partin et al. showed that the combination of Gleason score in the biopsy specimen, clinical stage and PSA provide the best separation to predict the final pathological stage. The analysis of 703 men undergoing radical prostatectomy resulted in probability curves and nomograms that can be helpful in making clinical recommendations for men with clinically localized prostate cancer [148]. In the most recent report the clinical and pathological data of 4133 men treated with radical prostatectomy in four different centers were combined and the nomograms were updated. In the validation analysis, 72.4% of the time the nomograms correctly predicted the probability of a pathological stage to within 10% [149]. This will enable patients and physicians to make more informed

treatment decisions. Nevertheless, the uncertainties around the pre-treatment evaluation are not excluded by using these nomograms. The development of improved sampling methods and better prognostic parameters is imperative.

Re-screening interval

The frequency of screening for any cancer is a compromise between unnecessary testing and the subsequent effects of false-positive testresults and the risk of missing curable cancer with less frequent testing. Prostate cancer screening has not been shown to be useful but is subject to study. Still, screening upon request takes place and optimization of all aspects of the detection procedure is desirable. Several studies have used a yearly re-screening interval. Mettlin et al. [88] reported on the annual detection rates in the first five years of the National Prostatic Cancer Detection Project of the American Cancer Society. These were respective 2.8%; 2.0%; 1.1%; 2.1% and 1.9% in the first to fifth screening round. In this study initially biopsies were not routinely taken at PSA levels above 4 ng./ml., later biopsies were taken if the elevated PSA could not be explained by benign gland enlargement. This may explain the relatively high detection rate in subsequent years. Cancers within the screening interval were not reported. Labrie et al. [150] described an initial detection rate of 3.4% With the use of a PSA cutoff of 3 ng./ml., DRE and TRUS. In the subsequent yearly visits the detection rates were 0.6%; 0.7% and 0.3% (TRUS was not used as a screening tool in the yearly re-screening visits). Smith and associates [151] observed a decrease in detection frequency from 3% below 1% after 48 months using PSA based screening with a cutoff of 4 ng./ml. and six-monthly re-screening. The proportion of clinically advanced cancer also decreased from 6% to 2%. The proportion of high-grade disease after surgery decreased from 11 to 6%. No interval cancers were detected.

To our knowledge no reports on interval cancers in prostate cancer screening are available which indicates that a one-year screening interval is too short. In a recent paper by Carter et al. a 2-year screening interval is suggested for men with PSA levels less than 2 ng./ml.. This was based on the observations that (1) PSA conversions in prostate cancer cases to greater than 5 ng./ml. when the initial level was less than or equal to 2 ng./ml. is rare (4%) within 2 years and (2) when the pretreatment PSA level is below 5 ng./ml. prostate cancer is highly likely to be curable [152]. Determination of the proper re-screening interval is mandatory. Answers may come from the European Randomized

study of Screening for Prostate Cancer where a 4-year re-screening interval is used and from further knowledge concerning PSA doubling time and tumor characteristics.

Treatment of prostate cancer

Early detection of prostate cancer can only be useful if treatment for localized prostate cancer is effective. Furthermore, the previously described reports on the natural course of clinically localized prostate cancer and deferred treatment series may give the impression that treatment is not necessary. Three options for therapy are commonly used: Radical prostatectomy, radiotherapy and deferred treatment or watchful waiting. There is still discussion concerning the optimal management of localized prostate cancer. In fact only two randomized treatment studies have been reported. The first study compares radical prostatectomy and watchful waiting [153]. No difference in overall survival after 15 years of follow-up was found. However, the study was never completed and lacks the necessary power as was recognized by the authors. One third of the included 142 patients were lost to follow-up and there was an imbalance in age between the two groups. Furthermore staging of the lymphnode status and bonescans were not performed. The second study compares radical prostatectomy and radiotherapy [154] and found a significantly lower progression rate after surgery. This study has also been criticized on methodological grounds. The randomization procedure was not entirely blinded, and the difference in the number of patients included in the treatment groups (56 received radiation and 41 underwent radical prostatectomy) is unexplained. Recently large randomized trials have been initiated to compare radical prostatectomy and watchful waiting [155,156] but their results will not be available for at least another decade.

The current opinions regarding treatment are based on a combination of personal observations and data from reports of uncontrolled studies. In absence of evidence attempts have been made to develop practical guidelines for treatment of patients with prostate cancer [157,158]. The outcome concerning survival and treatment complications allowed no conclusion. It was advised to use the information to inform newly diagnosed patients about the treatment options.

Comparison between radical prostatectomy and radiotherapy is hampered by differences in staging. Surgical staging includes a lymph-node dissection. In patients that are found to have positive lymphnodes a radical prostatectomy is not performed. Only a small

percentage of men treated with radiotherapy undergo a lymphnode dissection. If the lymphnode status is known to be negative the results of radiotherapy appear to be similar to surgical series [159]: 85% of patients were free of local disease at 10 years and 15% had died of PC. In a recent series the 10 and 15 year actuarial survival was 63.7% and 49.6% respectively. The cause specific survival was 84.2% and 80% respectively [160]. A further obstacle lies in the fact that prostate cancer is generally understaged at clinical examination. The clinical stage and biopsy grade are poor predictors for the pathological stage and grade. This might overestimate the benefit of radical prostatectomy. On the other hand the results of radical prostatectomy may be underestimated because surgically treated patients are usually younger and in better health. Albertsen et al. [34] have demonstrated that existing co-morbid disease is highly predictive of overall survival above and beyond patient age. Because of their lower mortality from other causes men treated by radical prostatectomy would have a greater opportunity to have a cancer-related death. This may lead to increased rates of metastases and death in surgically treated men, which may decrease apparent cancer-specific survival rates in comparison with other forms of therapy.

The results of radical prostatectomy in 2758 men with clinically localized prostate cancer were assessed in a multi-institutional pooled analysis by Gerber et al. [161]. Tumor grade appeared to be the most important preoperative factor in determining outcome. The disease specific survival 10 years following surgery were: 94% for grade 1, 80% for grade 2 and 77% for grade 3 disease. Metastases free survival at 10 years was 87%; 68% and 53% for the respective grades. Lu-Yao and Yao have carried out a survey of 59,876 prostate cancer patients treated by radical prostatectomy, radiotherapy or watchful waiting [162]. Again the cancer grade significantly affects overall survival. Patients with grade 3 disease had a much lower overall survival than their age-matched cohort in all treatment groups. The 10-year disease specific survival was poor in all three treatment groups as can be observed in table 4. The relative and disease specific survival however, were higher in the radical prostatectomy and radiotherapy group than in the deferred treatment group. The therapy options were assessed by intention to treat and treatment received to reduce bias because of exclusion from therapy of patients with positive lymphnodes. Staging, age and general health biases were not avoided. Comparison with the age matched cohorts shows that patients undergoing surgery have a higher overall survival than their age matched counterparts. This may be due to selection of healthier

patients for radical prostatectomy but it can not be excluded that the higher disease specific survival within this group also plays a role. Adequate adjustment for comorbidity is essential in comparison of overall mortality across treatment groups but its impact on prostate cancer specific survival is modest [34]. Thus the observed differences between the treatment options should be interpreted with caution.

Since grade 3 disease is associated with low disease specific survival whatever the treatment chosen, the question rises whether grade 3 disease is curable? Partin et al. [163] studied the outcome of 72 men with Gleason score 8-10 on needle biopsy. Twenty-nine of these men had positive lymphnodes. In the remaining men the actuarial likelihood of having undetectable serum PSA at 5 years was 43%. It was concluded that if the lymphnodes are negative, men with high-grade disease are suitable candidates for radical prostatectomy. With the proper evaluation some of the most aggressive tumors can be cured [164, 165].

	Intention to treat			*Treatment received*		
	Rp	*Rt*	*Wawa*	*Rp*	*Rt*	*Wawa*
G1	94 (91-95)	90 (87-92)	93 (91-94)	98 (97-99)	89 (87-92)	92 (90-93)
G2	87 (85-89)	76 (72-79)	77 (74-80)	91 (89-93)	74 (71-77)	76 (73-78)
G3	67 (62-71)	53 (47-58)	45 (40-51)	76 (71-80)	52 (46-57)	43 (38-48)

Table 4:

10-year disease specific survival-percentage with 95% confidence interval, in patients with clinically localized prostate cancer by intention to treat and treatment received. (Lu-Yao, Lancet 349, 1997 [162])

Abbreviations:

Rp=Radical prostatectomy; Rt=Radiotherapy; WaWa=Watchful waiting; G1=Well differentiated; G2=Moderately differentiated; G3=Poorly differentiated.

Adverse effects from treatment

Quality of life after cancer treatment has become a major issue in the choice of treatment. However, quality of life is not easy to assess. Litwin and co-workers used validated Health Related Quality Of Life (HRQOL) measures and new prostate –targeted items in three treatment groups (Radical prostatectomy (98 men); radiotherapy (56 men) and observation alone (60 men)) and compared the findings with an age matched cohort (273 men). They concluded that no differences were seen in general HRQOL. The

sexual, urinary and bowel function score in the disease-targeted HRQOL in both treatment groups differed significantly from the control group. The difference in scores between surgery and radiotherapy was not significant. The patients in the observation group experienced significantly more role limitations due to emotional problems than both treatment groups [166].

Incontinence, erectile dysfunction and bowel problems are often reported as adverse effects after treatment for prostate cancer. Table 5 shows a summary of four reports on adverse effects [167-170]. Variations seen depend strongly on criteria and methods of evaluation. Potency seems to be better preserved in patients receiving radiotherapy. In a report by Bagshaw et al. [171] on 900 patients treated by radiotherapy, potency was preserved in 86% of patients post-treatment and 50% of patients maintained erectile function 7 years post-therapy. Incontinence is more frequent in surgically treated patients whereas bowel problems are more pronounced in patients treated with radiotherapy.

	Wasson [166]		*Fowler* [167]	*Davidson* [168]	*Walsh* [169]
Therapy.	Radiation	Surgery	surgery	Surgery	Surgery
Mortality.	0.2%	1.1%	0.6%	1.5%	-
Any incontinence.	6.1%	26.6%	30%	5.9%	8%
Complete incontinence or artificial sphincter implant.	1.2%	6.8%	6%	6%	0.3%
Any bowel injury.	11.4%	2.7%	-	-	-
Bowel injury requiring long-term treatment.	2.3%	1.3%	-	-	-
Stricture.	4.5%	12.4%	20%	32%	
Impotence.	41.4%	84.6%	61%	57%	32%

Table 5:

Summary of four reports on adverse effects after treatment for prostate cancer.

Risks of screening

Serious complications of venous puncture, rectal examination and trans rectal ultrasound have not been described. The screeningtests are generally well accepted. The patients acceptance of the ultrasound guided trans-rectal biopsy procedure is very high, 70 to 92% of patients report no significant pain or discomfort during the biopsy procedure [172-174]. A process evaluation was carried out within the European Randomized study of Screening for Prostate Cancer [175]. This showed that 95% of all participants is willing to be re-screened. This indicates that patients are not experiencing too much discomfort from the screening procedure. The complications of the biopsy procedure have been described previously, as are the complications of treatment for prostate cancer. A second survey carried out by Fowler et al. [176] showed that 89% of patients would choose surgery again in spite of significant adverse effects. Eighty-one percent appreciated the treatment as positive. Expectant management is shown to increase anxiety among patients.

Comment

Considering the incidence and mortality of prostate cancer this disease forms a significant health problem. Furthermore, the impact of the disease is expected to increase in the near future because of the aging population and increasing awareness.
Once prostate cancer has spread beyond the prostate cure is generally impossible. The best treatment option is still under discussion, randomized studies are on their way but results are not expected within a decade.
It has been shown that early detection is technically possible but the optimal screening strategy has not been determined yet.
Stage reduction of screen detected prostate cancer has been described. This however, does not prove that early detection provides evidence for a cancer mortality decrease. Prostate cancer treatment is not successful in all cases. Lead- and length-time bias are closely related to the phenomenon of stage reduction.
The prevalence of prostate cancer in autopsy studies is high. It is estimated that 10 to 25% of these insignificant cancers are detected by the current diagnostic tests [37]. However, the detection of prostate cancer in the population is 4 to 5 times higher than the incidence of clinically diagnosed prostate cancer. More men are treated for the

disease than are at risk of dying from it. Part of the subsequent treatment may be considered overtreatment. Men who would not have died from the disease have a high chance of having to live with the adverse effects of treatment. However, it has been shown that men are willing to trade the reduction of risk of prostate cancer related death and mortality for adverse effects [176].

The prostate cancer incidence in the U.S.A. has risen dramatically, which is mainly explained by the increased awareness and early detection activities [8,9]. Recently declines in incidence have been reported in the Utah and Connecticut center of the Surveillance Epidemiology and End Result study areas of the National Cancer Institute of the United States (SEER) [177,178]. Furthermore a 6.3% decrease in prostate cancer mortality was observed [179]. This was more pronounced in men under age 75. In this group the decline was 7.4% whereas the decline in men over 75 amounted 3.1%. There has been no explanation for this phenomenon. The possibility that this trend is the result of early detection and treatment can not be excluded at this time.

Conclusion

At this moment it is unknown whether prostate cancer screening will reduce the mortality from this disease. This will have to be demonstrated in large prospective randomized studies such as the ones initiated in Europe and the United States of America [180].

Results however, are expected to be available about ten years from now in 2008. Men who wish to be screened should be carefully informed about the risks, adverse effects and potential benefits.

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Part A

Diagnostic Tools and their performance

Chapter II

Evaluation of PSA, DRE and TRUS in population based screening for prostate cancer: Suggestions to improve the efficiency of early detection*.

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Abstract

The value of Digital Rectal Examination (DRE), Trans-rectal ultra-sonography (TRUS) and of serum Prostate Specific Antigen (PSA) level as tools for the early detection of prostate cancer was evaluated to improve knowledge and skills in general and in order to optimize the screening protocol of the European randomized study of screening for prostate cancer (ERSPC).

Methods: Between July 1994 and January 1996 4,334 men aged 55 to 75 years old enrolled to the screening arm of the European randomized study of screening for prostate cancer (ERSPC) section Rotterdam and 3,963 underwent all three screening tests. Sextant biopsies were carried out in case of an abnormality in one or more tests.

Results: 172 cases of prostate cancer were found at a detection frequency of 4.3%. PSA proved to be the strongest predictor of prostate cancer. The value of DRE and TRUS is limited especially below a PSA value of 1 ng./ml. where 43 biopsies are necessary to find 1 case of prostate cancer.

To improve the performance of the screening procedure age specific reference ranges, PSA density and PSA pre-screening were applied to our biopsied population. Using Age specific reference ranges saves 14.3% of biopsies but 13% of prostate cancers will remain undetected. PSA-D with cut-off levels varying from 0.10 to 0.15 saves 14.5% to 30.5% of biopsies at the expense of respectively 5.3% to 22.9% of cancers detected. Pre-screening with PSA and omitting DRE and TRUS below a level of 1.8 ng./ml. saved 59.6% of screening-tests, 33.9% of biopsies and only 5.3% of detected cancers would have been missed within the screened population of 3,963 men.

* *Evaluation of PSA, DRE and TRUS in population based screening for prostate cancer: Suggestions to improve the efficiency of early detection. JBW Rietbergen, R Kranse, WJ Kirkels HJ de Koning, FH Schröder. British Journal of Urology 1997; Vol 79 (Suppl 2): 57-63.*

Conclusion: To improve the performance of the screening procedure, without losing a considerable amount of cancers, the most promising way would be not to perform the more laborious screening tests as DRE and TRUS under a PSA level of 1.8 ng./ml..

Introduction

In Europe prostate cancer is the second leading cause of male cancer deaths. In the Netherlands the morbidity and mortality caused by this tumor are exceeded only by those of lung cancer. In 1991, 4915 cases were discovered and 2222 deaths from cancer of the prostate were recorded in a male population of 7.5 million [1]. This health problem has been acknowledged in most of the western countries and efforts are being made to decrease Prostate cancer mortality. The possibility exists that screening for prostate cancer in asymptomatic men combined with early treatment may provide the answer. This however is a debated issue. In the USA and some European countries screening for prostate cancer is routinely applied to men at risk, in others, most northern European countries routine application of screening procedures for prostate cancer is not accepted [2].

The controversy over screening for prostate cancer hinges on whether or not early detection and treatment will reduce the mortality rate and what the adverse effects will be in terms of costs, anxiety and the morbidity and mortality of the screening tests, and treatment of the detected prostate cancers. In several European countries randomized screening studies are conducted with prostate cancer mortality as the major endpoint in order to prove or disprove the value of screening [3].

Three screening tests are available and are used in various combinations. The measurement of the serum prostate specific antigen (PSA) concentration, digital rectal examination (DRE) and trans- rectal ultrasonography (TRUS). PSA appears to be the most efficient test of the three [4], however, is not specific for prostate cancer since several non malignant conditions of the prostate are associated with elevated PSA levels as prostatic intraepithelial neoplasia [5], acute prostatitis [6], prostatic ischemia [7] and benign prostate hyperplasia [8]. Furthermore not all prostate cancers give rise to an elevated PSA concentration [9].

Reliable detection of clinically relevant but still confined prostate cancer cases is the goal of presently applied detection regimes. Unfortunately the specificity of the screening procedures is low which results in a considerable amount of "Low-Yield Biopsies". This

not only reduces the cost effectiveness but also increases the anxiety and morbidity within the screened population. Thus limiting the number of biopsies without loss of cancers detected would improve the efficiency and diminish the discomfort and health risks within the screened population.
We have assessed the screening tests and the biopsy rates (specified for the various screening tests and PSA levels) within the screened population of the ERSPC (Rotterdam).

Materials and Methods

Patient population.
Between July 1994 and January 1996; 8,668 men between 54 and 76 years old responded positively to a letter of invitation to enter the European Randomized Study of Screening for Prostate Cancer (Section Rotterdam). The only exclusion criterion is a previous diagnosis of prostate cancer. Written informed consent was obtained from all study subjects. Each participant filled out a questionnaire concerning their medical and family history. Those who responded were randomized to either the screening arm or the control arm. The men in the control arm were not tested in any way.
Of the 4,344 men in the screening arm 3,963 men underwent a serum PSA determination, digital rectal examination and transrectal ultrasonography. A suspicious finding by any of the three diagnostic tests prompted a sextant prostate biopsy.
Techniques:
All men underwent determination of serum PSA concentration (Hybritech Tandem-E PSA immunoenzymetric assay), blood samples were drawn before the other tests were performed. The cut-off level of the PSA test was set on 4.0 ng./ml., any value greater than 3.9 ng./ml. was considered elevated. At the time of screening the members of the screening team were not aware of the PSA results.
Digital rectal examination was performed by a resident urologist or an ultrasound technician, nodularity, induration and asymmetry were considered abnormal.
Biplanar transrectal ultrasonography was performed by a resident urologist or an ultrasound technician, using a Bruel & Kjaer® model 1846 mainframe and a 7 MHz biplanar endorectal transducer, with the subject in the left lateral decubitus position. The sonographic criteria for prostate cancer described by Lee et al. were used [10]. For each subject the length, width and height of the total prostate and transition zone was

determined as well as the volume. Volumetry was obtained using 5-mm step section planimetry.

All prostate biopsies were done by a resident urologist with ultrasound guidance, using a Manan pro-mag® 2.2 biopsy gun and an 18 gauge Bard® biopsy needle. If the biopsy indication was an elevated PSA level or an abnormal digital rectal examination sextant biopsies were performed. In case of a hypoechoic lesion, the lesion was sampled in addition to the sextant biopsy. All subjects received antimicrobial prophylaxis (Co-trimoxazole 960 mg).

The pathological findings from sextant and ultrasound guided biopsies were the reference test for determining the presence or absence of prostate cancer.

Statistical analysis:

A multivariate analysis was performed for 7 parameters: Age at entry; digital rectal examination; positive family history for Prostate cancer (from the baseline questionnaire, not verified); log prostate specific antigen; log total prostate volume; log transition zone volume and trans-rectal ultrasonography. Within the biopsied group of subjects we derived predictors for biopsy outcome (cancer or no cancer) from all single parameters studied and several combinations (including all bivariate possibilities) by means of logistic regression analysis [11]. The sensitivity and specificity were calculated as well as the receiver operating characteristic curve that depicts the reciprocal relation between sensitivity and specificity by plotting true positive (sensitivity) versus false positive (1 minus the specificity) results, as a function of subsequent PSA cutoff values. [12]. We compared the efficacy of the predictors thus obtained by means of the area under the ROC curve [13]. The predictor value represents the chance on a correct answer in a two alternative forced choice (cancer or no cancer) within the biopsied population (with a maximum value of 100).

In the Venn diagrams (Fig. 1 and 2) the biopsies taken and cancers found are shown and specified for all three screening tests as well as for their various combinations. Within our screening procedure each of the 7 fields represents a reason for biopsy. To estimate the reduction in the number of biopsies taken, one field or a combination of fields could be excluded. The number of biopsies saved and the number of cancers lost can be read from the Venn diagram. This procedure can be repeated for all possible combinations ($2^{(7)} = 128$). If one or more pre-screen PSA values are added the number of possible combinations doubles or increases accordingly.

In this analysis these 128 possible screening algorithms were evaluated and also the combination of the algorithms with other conditions which have been described in the literature and which may reduce the number of biopsies: Age specific reference ranges [15] and PSA-density [14]. In addition PSA-cut-off levels under which no biopsy should take place were assessed for PSA =0 to PSA = 4 ng./ml. with increments of 0.1. For all possible combinations the cancers lost and biopsies won were calculated.
The evaluation of the ratio of free and total PSA is subject to two other reports [16][17].

Results

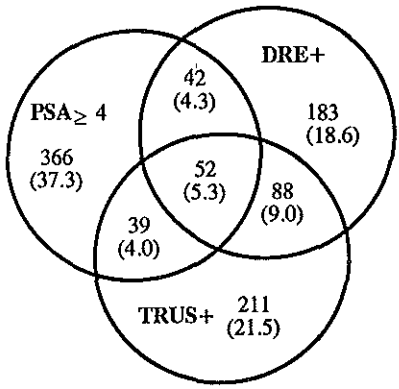
Population:
The mean age of the men in this screening population was 64.2 (range 54-76), the median age was 64. Of the 4,344 subjects in the screening group 3,963 men underwent all screening tests. In 1050 (26.5%) subjects there was an indication for biopsy. In table 1 the age distribution of subjects enrolled and those who underwent a biopsy is shown. In 69 cases the biopsy was not performed for various reasons: 42 men refused a biopsy and will be rescreened after 1 year, 24 men could not be biopsied for medical reasons and 3 biopsies are pending. Table 2 shows the PSA distribution within the screened population. It should be noted that 86.6% of all subjects had PSA levels less than 4 ng./ml.. The median PSA value was 1.4 ng./ml. (cancers included).

Age	*<55*	*55-59*	*60-64*	*65-69*	*70-75*	*≥75*	*total*
Screened	1	1137	959	925	842	99	3963
Biopsies	0	197	204	290	257	33	981

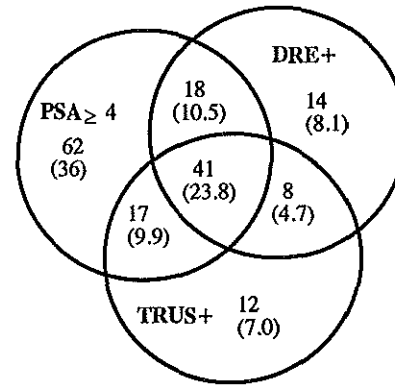
Table 1:
Age distribution and number of subjects enrolled and number of biopsies.

Cancer detection:

A total of 981 biopsies were performed and 172 cases of prostate cancer were found resulting in an overall detection rate of 4.3 %. The prostate volume was measured in 967 of all biopsied men in whom 170 cases of cancer were detected. The performance of the various screening tests expressed in number of biopsies and number of cancers found is detailed in two Venn diagrams (Fig.1). A total of 499 men had PSA levels ≥ 4 ng./ml., in this group 138 (80.2%) cancers were found. 482 men had PSA levels < 4 ng./ml. and 34 (19.8%) cancers were found. The median PSA value within the prostate cancer group was 6.2 ng./ml. versus 1.3 ng./ml. within the biopsied group without the diagnosis of cancer.



Biopsies (%) N= 981



Cancers (%) N= 172

Fig. 1

Number of biopsies specified per screening test or combination of tests.
Number of cancers detected, specified per screening test or combination of tests. Each circle represents a screening-test. The overlapping fields represent combinations of the tests.

Biopsy rates:

Fig.2 shows the number of biopsies performed for each cancer detected specified per screening test or combination of tests.

At PSA levels ≥ 4 ng./ml., 3.6 biopsies were performed to find one cancer. At PSA levels less than 4 ng./ml., 14.2 biopsies were required.

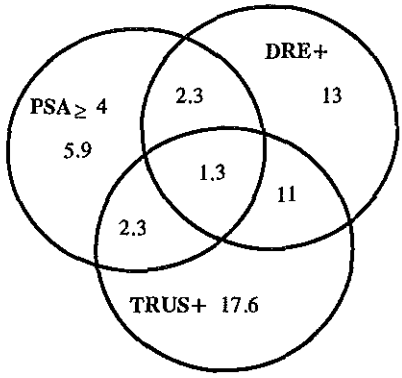


Fig 2:

Number of biopsies performed to detect one prostate cancer.

Table 2 shows the biopsy rates in various PSA ranges as well as the cancer detection in those ranges. The number of biopsies necessary to find one cancer are specified in the last row of the table. In the range 0-1 ng./ml., 43 biopsies had to be performed to find one cancer. In the range 1-2 ng./ml., 18.7 biopsies were performed to detect one cancer.

PSA RANGE	*0-1*	*1-2*	*2-3*	*3-4*	*0-4*	*4-10*	*≥10*	*TOTAL*
Screened #	1372	1270	511	278	3431	447	85	3963
Screened %	34.62 %	32.05 %	12.89 %	7.01 %	86.6%	11.28 %	2.15 %	100 %
Biopsies #	172	187	84	39	482	421	78	981
Biopsies %	17.5 %	19.1 %	8.6 %	4.0 %	14%	42.9 %	8.0 %	100 %
Cancer #	4	10	12	8	34	93	45	172
Detection %	0.3 %	0.8 %	2.3 %	2.9 %	1%	20.8 %	53 %	4.3 %
biopsies/Pc	43	18.7	7	4.9	14.2	4.5	1.7	

Table 2:

PSA distribution for the screened population, biopsied population, population with prostate cancer, detection rate and number of biopsies performed to detect one case of prostate cancer.

Multivariate analysis:

In table 3 the predictor values are shown for all 7 parameters that were tested as well as for all bi-variate combinations. The highest value for a single parameter was found for log PSA (77). Of the combined tests log PSA and log total prostate volume showed a value of 82. The predictor value was 80 for the multivariate combination of the three screening tests used in our study (DRE, TRUS and log PSA). The area for the combination of all 7 parameters was 84 which was the same as for the combination of log PSA, DRE, TRUS and log volume.

P	*AGE*	*DRE*	*FAM*	*logPSA*	*logVOL*	*logTZV*	*TRUS*
	53	56	51	77	53	53	53
AGE	-	57	54	77	57	57	55
DRE	-	-	56	79	58	57	56
FAM	-	-	-	77	55	55	54
logPSA	-	-	-	-	82	82	79
logVOL	-	-	-	-	-	53	55
logTZV	-	-	-	-	-	-	55
TRUS	-	-	-	-	-	-	-

Table 3:

Predictor values for 7 parameters and their combinations .

Abbreviations:

AGE=Age at entry of the study; DRE=Digital rectal examination; FAM=Positive family history for prostate cancer; LogPSA=Logarithm of the serum PSA value; LogVOL=Logarithm of the total prostate gland volume; LogTZV=Logarithm of the transition zone volume; TRUS=Transrectal ultrasonography.

Statistical analysis:

Age specific reference ranges were applied on the population with PSA levels ≥4 since all subjects underwent a biopsy. In this PSA range 22 cases of prostate cancer would have been lost and 829 of 967 biopsies would have been performed to find 148 cancers (table 4).

Age range	*PSA Cut-off*	*Cancers ERSPC*	*Cancers lost*	*Percentage lost*
60-69	4.5 ng./ml.	76	12	7%
70-79	6.5 ng./ml.	39	10	5.9%
TOTAL		115	22	12.9%

Table 4:

PSA Reference ranges (Oesterling et al. JAMA 270, 1993.) applied to ERSPC cancer detection.

PSA-Density (PSA level divided through the total prostate volume (PSA-D)) was determined for all men with PSA levels ≥4 ng./ml. with or without an abnormal DRE and/or TRUS. In table 5a the number of biopsies avoided and cancers lost are shown, for various PSA-D levels, with an increment of 0.01 when applied on all men with PSA levels ≥4. Table 5b is the same table however the PSA-D is only applied to men with normal DRE and TRUS findings. If prostate cancer was diagnosed in this subset, the stage will be T1C.

The use of PSA pre-screen cut-off levels is further specified in Fig. 3 where cut-off levels with increments of 0.1 ng./ml. and their relation to the percentage of screened men, biopsies done and cancers detected are plotted. This was done for the population with PSA levels <4 ng./ml.. In this range 3430 men were screened (3396 men without the diagnosis of prostate cancer), 482 biopsies were done and 34 cases of prostate cancer were detected.

	a] N=967		*b] N=967*	
PSA-D	*Bx avoided(%)*	*PC lost (%)*	*Bx avoided(%)*	*PC lost (%)*
0.06	22 (2.3)	1 (0.6)	18 (1.9)	1 (0.6)
0.07	43 (4.5)	1 (0.6)	37 (3.8)	1 (0.6)
0.08	63 (6.5)	3 (1.8)	51 (5.3)	2 (1.2)
0.09	104 (10.8)	5 (2.9)	87 (9.0)	2 (1.2)
0.1	140 (14.5)	9 (5.3)	112 (11.5)	3 (1.8)
0.11	174 (18.0)	13 (7.6)	140 (14.5)	7 (4.1)
0.12	210 (21.7)	19 (11.1)	171 (17.7)	13 (7.6)
0.13	244 (25.2)	30 (17.6)	197 (20.4)	21 (12.4)
0.14	271 (28.0)	34 (20.0)	220 (22.8)	23 (13.5)
0.15	295 (30.5)	39 (22.9)	239 (24.7)	24 (14.1)
0.16	321 (33.2)	44 (25.8)	257 (26.6)	25 (14.7)
0.17	342 (35.4)	51 (30.0)	272 (28.1)	29 (17.1)
0.18	355 (36.7)	54 (31.8)	281 (29.1)	30 (17.6)
0.19	377 (39.0)	62 (36.5)	299 (30.9)	34 (20.0)
0.2	387 (40.0)	68 (40.0)	305 (31.5)	37 (21.7)

Table 5:

a: Number of biopsies avoided and prostate cancers lost when PSA-D would have been applied to the biopsied population with PSA levels ≥4 ng./ml. with or without abnormal DRE and/or TRUS findings.

b: Number of biopsies avoided and prostate cancers lost when PSA-D would have been applied to the biopsied population with PSA levels ≥4 ng./ml. with normal DRE and/or TRUS findings.

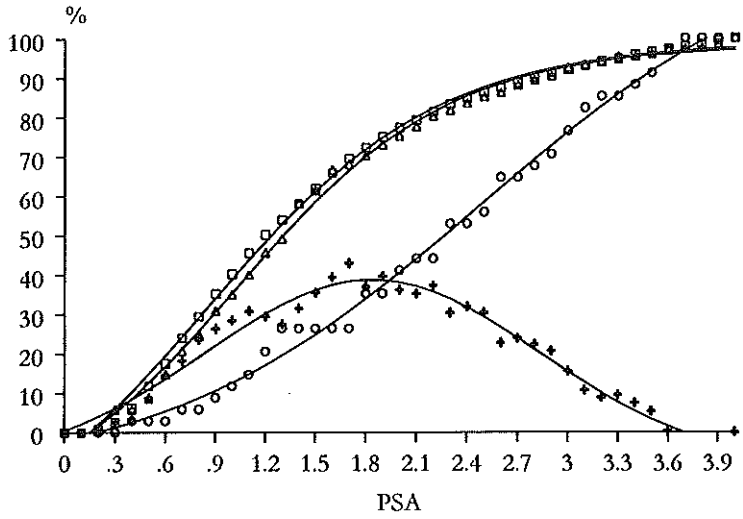


Fig 3:

A: □ *Cumulative percentage of men screened N=3430.*

B: ○ *Cumulative percentage of men with prostate cancer N=34.*

C: Δ *Cumulative percentage of men that underwent a biopsy N=482.*

D: + *Cumulative percentage of men screened/biopsied minus Cumulative percentage of men with prostate cancer.*

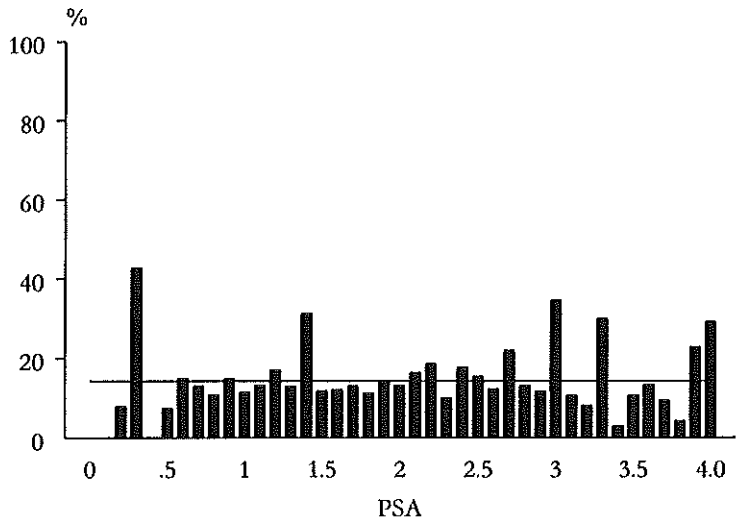


Fig.4:

Percentage of biopsies and men screened specified for PSA levels from 0 to 4 ng./ml. with increment of 0.1 ng./ml.. Fitted line: y = 14.3 (Standard error = 1.4)

Discussion

In evaluating the screening procedure that is used within the ERSPC section Rotterdam the most important step has been simply counting all cancers and all biopsies specified for PSA level, age and screening test. The first observations indicate that PSA is the most powerful tool available for an early diagnosis of prostate cancer. The Venn diagrams (Fig 1 and 2) show that most cancers (80.2%) were found within the PSA range ≥ 4 ng./ml.. The biopsy rates indicate that within this PSA range only 3.6 biopsies had to be performed to find one case of prostate cancer. At PSA levels < 4 ng./ml. 14.2 biopsies were necessary to find 1 cancer. This is further specified in table 2, an increase in PSA level leads to a decrease in the number of biopsies that has to be performed for the diagnosis of one case of prostate cancer. The cancers that were found through positive DRE or TRUS findings alone (at PSA levels <4) formed respectively 8.1% and 7% of cancers detected. If PSA would not have been used as a screening test DRE could have detected 47.1 % of all cancers. TRUS would have detected 45.3 %. The combination of DRE and TRUS would miss 36 % of all cancers (The stage T1C tumors) whereas the use of PSA alone would only miss 19.8 % of cancers diagnosed.
Within the biopsied subpopulation we performed a multivariate analysis. The results are shown in table 3. It should be noted that the results derived from this statistical procedure are only applicable to the biopsied population. The indication for performance of biopsies is clearly very broad resulting in a high overall biopsy rate (24.7 %). The statistical analysis concerns a relatively large sample of the total screened population. There is a reasonable ground that the conclusions based on this biopsied sample of men may be extrapolated to the general screened population. Again it becomes clear that PSA performs better than the other parameters with a predictor value of 77. Age at entry, positive family history for prostate cancer, TRUS and log prostate and transition zone volume are poor predictors. DRE is performing slightly better. If log prostate volume is added to the PSA test the performance improves (the predictor value increases to 82), this is also true for the combination of the 3 screening tests in combination with log prostate volume (predictor value of 84). Adding age does not improve the performance of PSA and has a minimal effect on DRE and TRUS.
To improve the performance of the screening procedure, i.e. to avoid unnecessary biopsies we might conclude from the above that adding volume would have a beneficial effect on the screening procedure. Benson and co-workers recommended the use of

PSA density (PSA value divided by the volume of the prostate) [14] to discriminate between BPH and prostate cancer. Using a cut off level of 0.15 could have saved 295 unnecessary biopsies but 39 cases of prostate cancer would not have been detected Using a cut off level of 0.10 could have saved 140 unnecessary biopsies but 9 cases of prostate cancer would not have been detected. The use of PSA-D will reduce the number of unnecessary biopsies, which explains the favorable predictor value of this combination, however 5.3% and 22.9% of cancers would not have been detected using PSA-D cutoff levels of respectively 0.1 and 0.15 ng./ml./cc.

Including age in the screening procedure did not improve the performance in our multivariate analysis. Oesterling et al. recommend the use of age specific reference ranges [15] which are specified in Table 7. The use of various PSA cut-off values within age specific reference ranges are applied to our population using the same method as Oesterling and co-workers did [18]. The range of 40-49 is not included in our study. The range 50-59 with a PSA cut-off level of 3.5 ng./ml. is not easily evaluated because biopsies were only performed in case of DRE and/or TRUS abnormalities between PSA levels of 3.5 and 4 ng./ml.. We have chosen to limit the evaluation of the age specific reference ranges to the PSA range where all subjects were biopsied in order to avoid speculations. In this group we would lose 22 cancers and save 138 (14.3%) biopsies. If we would apply these age-specific reference ranges on our population we are missing 12.9% of detected cancers. Saving 138 biopsies when using PSA-D with a cutoff of 0.1 would be at the expense of 13 cancers less.

In the Rotterdam section of the ERSPC all three screening tests were used and weighed equally in the decision whether biopsies should be taken. If we look at the performance of the various tests we can conclude that DRE and TRUS are poor predictors for prostate cancer, this is especially true for PSA levels below 4 ng./ml.. To reduce the "low yield" biopsies most is to be gained in this range since only 19.8% of all cancers were found in a group of men that amounts to 86.6% of the screened population. For this reason we focused on this PSA range. In Fig. 3 the cumulative percentages of men screened, men biopsied and men with a biopsy positive for prostate cancer are plotted. The graphs for men screened and biopsies done show a striking overlap, which is explained by the fact that there is a linear relation between the number of biopsies taken and the composition of the population (Fig. 4). This relation is best described through the line y = 14.3 (Standard Error 1.4). DRE and TRUS abnormalities are obviously

spread equally over the population and the fact whether prostate cancer is found depends on the PSA value within this subset of men. This does not automatically mean that DRE and TRUS have no discriminating properties because the men that had normal DRE and TRUS findings were not biopsied. It remains unknown whether clinically relevant prostate cancer is present in these men and what the number of cancers will be that can be detected through sextant biopsies of the prostate. The only way to evaluate the true value of DRE and TRUS for prostate cancer detection in the PSA range <4 ng./ml. would be to biopsy a random sample of the population and study the predictive potential of the screening modalities with respect to biopsy outcome (golden standard). However, ethically this would be a very complex issue.

The graph showing the number of prostate cancers detected is also a sigmoidal curve. To determine where the efficacy is maximal (i.e. where minimal loss of detected prostate cancers yields the maximal percentage of biopsies won and men screened less) the curves were subtracted. Curve D shows that the efficacy is maximal at a PSA value of 1.7 ng./ml.. At this cutoff value 328 biopsies (33.9%) are won at the expense of 9 cases (5.3%) of prostate cancer lost. Also 2361 men (59.6%) will have to be screened through PSA only instead undergoing DRE and TRUS in addition. From a PSA level of 1.8 onwards the number of cancers diagnosed is rising and less biopsies are necessary to diagnose one case of prostate cancer.

These observations have led to a change in the study protocol. Since the maximum of curve D still shows variations because of the small numbers of cancers detected in the PSA range under four, on which the curve is based we have chosen a PSA pre-screen cutoff value of 1 ng./ml.. Raising the cutoff value is under consideration.

Screening for prostate cancer is still a controversial issue, clinicians in many European countries conclude that screening is premature and that the effect of early detection and treatment will have to be studied in randomized screening studies with prostate cancer mortality as a major endpoint [2]. The purpose of early detection regimes should be to detect the cancer in a locally confined stage where it can be cured.

The final analysis of this study can only be made based on the survival within both the screened and the control group. The clinical relevance and outcome of tumors found at PSA levels below 4 ng./ml. should be assessed, as an endpoint of the study when the PSA specific survival of detected prostate cancers is known. As long as the natural history of these tumors is not sufficiently known, it is unfavorable to ignore this subset because these tumors are locally confined and may contribute to the survival rate.

On the other hand 43 biopsies, the number of biopsies needed to detect one prostate cancer in the PSA range < 1 ng./ml. is unacceptable in terms of anxiety and risk of complications within this group of subjects. The loss of 2.3% of prostate cancers is of minimal relevance for the outcome of the study and will save 17.5 % of biopsies and 34.6% of the more laborious screening tests.
If we compare this to the use of PSA-density, age-specific reference ranges or omission of TRUS or DRE the gain in screening tests and biopsies not performed is less. However since the gain in survival has to come from early detection of prostate cancer to find the tumor in a locally confined stage we think it is unfavorable to lose too many detected cancers before we are able to determine their clinical relevance.

Conclusion

PSA as a screening tool is strongest predictor for prostate cancer.
In the PSA range ≥4 ng./ml. PSA-D is more efficient in diminishing the number of biopsies performed to detect one prostate cancer than the use of age specific reference ranges. It is also more laborious and expensive since the prostate volume has to be known.
The frequency distribution of serum PSA in the screened population shows that most men have PSA levels <4 ng./ml. and the biopsy prostate cancer rate is very high in this range.
A PSA pre-screen cut-off level of 1.7 ng./ml. under which no further tests should take place is the most efficient method to diminish the number of more laborious screening tests as DRE and TRUS and biopsies within our population. Only 5.3% of detected cancers will be lost.

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Chapter III

The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population*.

Chris H. Bangma, John B. W. Rietbergen, Ries Kranse, Bert G. Blijenberg, Kim Petterson And Fritz H. Schröder.

Abstract

The ratio between free and total prostate specific antigen (PSA) in serum improves the specificity of total serum PSA for the detection of prostate carcinoma in select populations. The value of the free-to-total PSA ratio for a PSA of 4.0 to 10.0 ng./ml. was analyzed in a screening population.

Materials and Methods: From 4,800 participants 55 to 76 years old 977 biopsies were obtained because of an abnormal digital rectal examination, suspicious transrectal ultrasonography and total serum PSA 4.0 ng./ml. or more. Of 191 patients with prostate carcinoma detected 101 had a serum PSA of 4.0 to 10.0 ng./ml. and 54 of them underwent radical prostatectomy. A free-to-total PSA ratio of 0.20, age specific PSA reference ranges and a PSA density of 0.12 ng./ml./cc were evaluated for the ability to increase the specificity of total serum PSA in predicting positive prostate biopsy results.

Results: Receiver operating characteristics curves for the free-to-total PSA ratio showed a significant increase in specificity compared to PSA. Retrospective application of age specific PSA reference ranges, the free-to-total PSA ratio and the PSA density decreased the number of biopsies significantly by up to 40% in our study, with a decrease in cancer detection rate of 12%. When used in combination with digital rectal examination, the pathological stage of undetected carcinomas appeared favorable.

Conclusions: The free-to-total PSA ratio may be used to decrease the number of biopsies in patients with an intermediate PSA of 4.0 to 10.0 ng./ml.

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* *The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for postate cancer in the general population. ChH Bangma, JBW Rietbergen, R Kranse, BG Blijenberg, K Petterson, FH Schröder. Journal of Urology 1997; vol 157: 2191-2196.*

Introduction

Screening for prostate cancer is usually performed by determination of prostate specific antigen (PSA) and digital rectal examination. Transrectal ultrasonography can be added for ultrasonic lesion detection and prostate volumetry. Selection of candidates for prostate biopsy is complicated by the fact that all screening modalities and their combination lack sufficient specificity, resulting in a high ratio between the number of biopsies obtained and the number of detected carcinomas. In most screening studies overall approximately 5 biopsies are needed to detect 1 carcinoma [1-5]. To increase the specificity to predict positive prostate biopsies, PSA has been adjusted to prostate volume (PSA density) and age (age specific reference ranges) [6, 7].
The free-to-total serum PSA ratio offers a new parameter to increase the specificity of total serum PSA to detect prostate cancer in select patients [8-10] and in a screening population [11]. In previous studies a simulated case selection for biopsy was performed in a well-defined screening population to analyze simultaneously the value of free-to-total PSA ratio, age specific PSA reference ranges [12] and PSA density [13] for the detection of prostate cancer. In those studies and in others in which these factors were not compared to each other [14] no significant increase in specificity was obtained for the application of free-to-total PSA ratios compared to total serum PSA. Also no subgroups within the studied population could be identified in which application of the free-to-total PSA ratio showed a clinical or statistically significant advantage. We analyzed the value of the free-to-total PSA ratio for screening prostate cancer in men with an intermediate PSA of 4.0 to 10.0 ng./ml., and simultaneously compared these values to age specific PSA reference ranges and PSA density.

Patients and methods

We studied 4,800 consecutive participants (55 to 76 years old) of the Rotterdam site of the European Randomized Study of Screening for Prostate Cancer [4] who had been randomized to undergo total serum PSA determination (Hybritech Tandem-E assay (Hybritech Inc., San Diego, Ca, USA.), digital rectal examination and transrectal ultrasonography of the prostate. Blood sampling was done before further testing. Digital rectal examination was performed before transrectal ultrasonography by 1 of 5 well trained Urological residents without knowledge of the PSA values. An ultrasound

machine with a 7.0 MHz. Biplanar probe was used for diagnostic ultrasonography, and planimetric volumetry of the prostate gland and its inner zone.

Ultrasound guided systematic sextant biopsies were obtained in case of a suspicious digital rectal examination and/or transrectal ultrasonography, and/or PSA greater than 4.0 ng./ml. An additional biopsy of any hypoechogenic lesion was obtained.

Prostate cancer was detected in 191 men. All men with a negative biopsy and those in whom no biopsy was obtained were considered free of prostate cancer. The biopsy results were used to assess the validity of the free-to-total PSA ratio in combination with total PSA to detect prostate carcinoma, and were considered to indicate the definitive histological status for the individual. All 432 participants with an intermediate PSA of 4.0 to 10.0 ng./ml. underwent biopsy and results were analyzed according to the free-to-total PSA ratio, PSA density and age specific reference ranges. A case selection simulation procedure was used to evaluate the relative value of these 3 factors as indicators for biopsy. The cutoff values chosen were a free-to-total PSA ratio of less than 0.20 [11] and PSA density of 0.12 ng./ml./cc or more [6]. The histological results of men who underwent radical prostatectomy (after pelvic lymphadenectomy with perioperative frozen section) were classified as organ confined (stage T2 N0 M0, grades 1 to 3) and extensive (stages T3 to 4 N0 M0 grades 1 to 3) disease.

Age specific reference ranges for total serum PSA were determined with the ProStatus-TM (Delfia, Turku, Finland) PSA free/total assays using the 95th percentile upper limit of total PSA values (mean + 1.65 standard deviations) in men without prostate cancer [12, 15]. Classification was by age ranges of 5 years (table 1). Also the 95th percentile lower limit of the free-to-total PSA ratios was calculated to illustrate the age dependency.

Age (yrs)	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*
Hybritech assay [12]	3.5		4.5		6.5
ProStatus-TM assay					
Total PSA	3.8	4.3	4.9	5.5	6.3
Free PSA	0.87	0.96	1.1	1.2	1.3
Free-to-total PSA ratio:					
PSA 0-200	0.14	0.14	0.14	0.14	0.14
PSA 4-10	-	0.10	0.11	0.12	0.12

Table 1:
Age specific reference ranges for PSA (ng./ml.) in 1,659 men without prostate carcinoma

In all 991 participants who underwent prostate biopsies the free-to-total PSA ratio was determined by retrospective application of the Delfia ProStatus-TM PSA free/total assay. Serum samples had been stored at –70°C. The assay provides simultaneous dual label measurement of free and total PSA by using time resolved fluorimetry of europium (free PSA) and samarium (total PSA) chelates. This assay measures free and complexed PSA in an equimolar fashion. The detection limits for the dual label assay are less than 0.01 and less than 0.1 ng./ml. for free and total PSA, respectively. The coefficients of variation were 7.2 to 4.3% at serum concentrations of 0.7 to 70.7 ng./ml. for total PSA, and 10.3 to 3.7% at serum concentrations of 0.17 to 35.5 ng./ml. for free PSA during 22 days, with 6 control samples supplied by the manufacturer [14].

The ProStatus-TM and Tandem-E assays proved to correlate well for a wide range, with coefficients of correlation of 1.00 for 67 men with and 0.99 for 1,659 men without prostate cancer [15-17]. Although both assays claim to be equimolar, they make use of different antigenic sites and antibodies. Therefore, we stress that results of PSA measurements with these 2 assays are not interchangeable by definition.

Receiver operator characteristics curves were used to show the relative intrinsic discriminatory potential of the various parameters as predictors for a positive biopsy result. These predictors were estimated as a function of the various continuous parameters and of binary parameters, such as digital rectal examination and transrectal ultrasonography, by means of logistic regression analysis.

Results

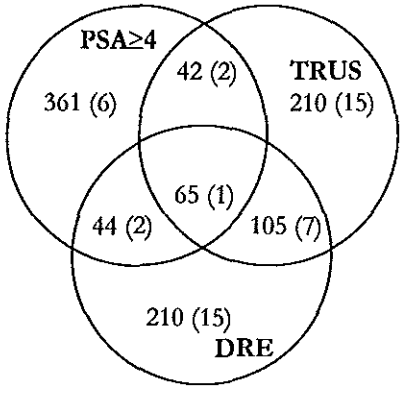
General characteristics of all men are shown in table 2. In 4,800 men 191 cancers were diagnosed histologically by 977 sextant prostate biopsies (cancer detection rate 4.3%). There was no significant difference between the median prostatic volume of men with and without prostate carcinoma (Mann-Whitney U test). Therefore, no sampling advantage by biopsy for smaller prostates occurred.

Venn diagrams were used to describe the indications for the 977 biopsies performed and the subsequent number of cancers detected for each indication (fig. 1). In 1 biopsy the transrectal ultrasonography result was not noted. The ratio of number of biopsies-to-number of carcinomas is depicted between brackets. The low yield of diagnostic transrectal ultrasonography for detection of prostate cancer at a PSA of less than 4.0 ng./ml. is apparent.

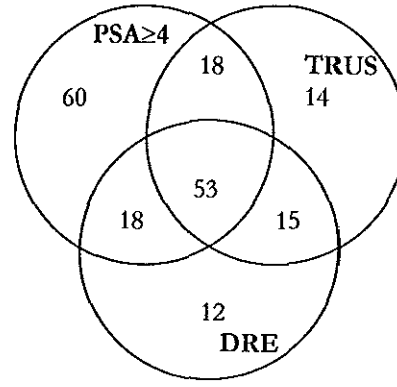
	Negative biopsies			Positive biopsies			*P Value*
	No. Pts.	*Median*	*(Range)*	*No. Pts.*	*Median*	*(Range)*	*Mann Whitney U test*
Age (yrs)	786	67	(55-77)	191	67	(55-76)	0.13
Prostate volume (cc)	781	38.2	(10.9-224.6)	187	34.9	(15.4-106.8)	0.18
Transition zone volume (cc)	781	20.3	(2.2-166.7)	187	18.2	(3.3-82.2)	0.06
Study PSA (ng./ml.)	786	3.0	(0.1-49.4)	191	6.1	(0.3-304)	<0.001
ProStatus-TM assay (ng./ml.)							
Total PSA	786	2.8	(0.09-35.2)	191	6.13	(0.45-272.9)	<0.001
Free PSA	786	0.57	(0.00-8.43)	191	0.85	(0.09-17.37)	<0.001
Free-to-total PSA ratio	786	0.23	(0.00-0.78)	191	0.13	(0.04-0.57)	<0.001

Table 2:

Age, prostate volumes and PSA values in 977 participants with 786 benign and 191 prostate cancer biopsies.



Biopsies #, (Biopsies/cancer) N = 976



Cancers # N = 190

FIG. 1:

Venn diagrams illustrate distribution of indications for prostate biopsy in 4,800 men, and number of cancers detected by digital rectal examination (DRE), transrectal ultrasonography (TRUS) and serum PSA of 4.0 ng./ml. or more. Numbers in parentheses indicate rounded number of biopsies needed to detect 1 cancer (ratio of number of biopsies-to-number of prostate cancers). A, number of biopsies. B, number of cancers detected.

Figure 2 shows the distribution of PSA values (ProStatus-TM assay) and the free-to-total PSA ratio in 977 men who underwent prostate biopsies. In table 1 the age specific reference ranges of PSA and the free-to-total PSA ratio were calculated for 1,659 men 55 to 74 years old without prostate carcinoma [11]. In our sample of 331 men of the same age without prostate cancer and with a PSA of 4 to 10 ng./ml. there was an age dependency for free-to-total PSA ratio as shown by a linear regression formula of: free-to-total PSA ratio = 0.003 x age (standard deviation 0.001) - 0.021 (standard deviation 0.046). The median free-to-total PSA ratio per 5-year age group was only significantly different compared to an age group at least 10 years older or younger. Of note is that the 95th percentile lower limit of the free-to-total PSA ratio for the complete range of PSA was identical for each age group (0.14), while that calculated for a PSA of 4 to 10 ng./ml. was somewhat less. However, there were no significant differences between these lower limits (table 1).

Receiver operating characteristics curves of total serum PSA and the free-to-total PSA ratio were constructed for all 432 men undergoing biopsy with a PSA of 4.0 to 10.0 ng./ml., including 101 with cancer (fig. 3). A significant difference (2 standard errors) was obtained between the area under the curve for the free-to-total PSA ratio and that for total serum PSA. Figure 3 also shows the receiver operating characteristics curves for the combination of PSA and digital rectal examination, or the combination of PSA, free-to-total PSA ratio and digital rectal examination as indicators for biopsy in the intermediate PSA range. Digital rectal examination added significantly in relative diagnostic potential compared to PSA only, increasing the area under the curve by 7%. The combination of PSA, free-to-total PSA ratio and digital rectal examination showed the largest area under the curve, which was significantly different from other combinations and increased the area under the curve of PSA only by 14%.

Table 3 shows the result of a case selection simulation procedure in which digital rectal examination, free-to-total PSA ratio, PSA density or age specific reference ranges were applied according to the aforementioned cutoff values as indicators for biopsy (instead of the indicator of total PSA of 4.0 ng./ml. or more) for men with an intermediate PSA range.

In 5 of 432 such men the ultrasound results were not complete so that 427 men were included in the study. All men underwent systematic sextant biopsies. Those with a hypoechogenic lesion underwent a seventh biopsy through the lesion.

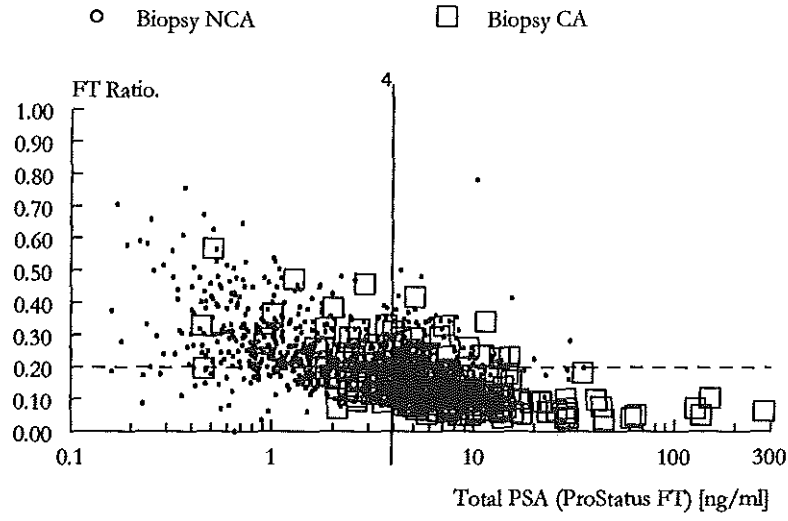


FIG.2.

Distribution of total PSA (ProStatus-TM assay) and free-to-total PSA ratio (F/T) in 977 men who underwent prostate biopsies, including 191 with cancers (CA). NCA, no cancer.

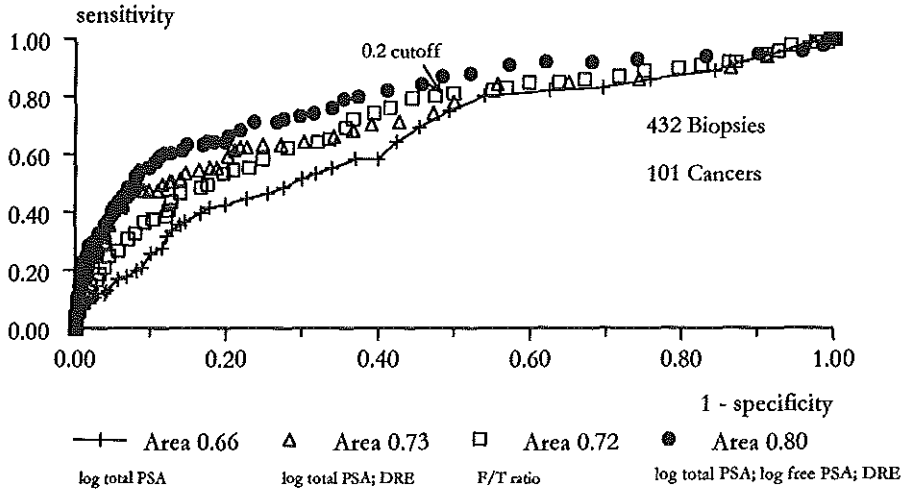


FIG.3.

Relative effectiveness of diagnostics illustrated in receiver operating characteristics curves of 432 men with PSA of 4.0 to 10.0 ng./ml. (standard error of areas 0.03). DRE, digital rectal examination. F/T ratio, free-to-total PSA ratio.

Diagnostic transrectal ultrasonography was a poor predictor for biopsy outcome and therefore not analyzed in table 3. The distribution of organ confined and extended carcinomas according to the histological results after radical prostatectomy in men not selected (lost to detection) by the combination of parameters is shown in table 3. Using digital rectal examination only as an indication for biopsy in the intermediate PSA range 57% of tumors would not have been detected. With free-to-total PSA ratio only as a biopsy indicator 44% of biopsies would not have been performed, with 19% of cancers not detected. The number of lost cancers could be significantly improved by the addition of digital rectal examination. Only 12% of cancers would have remained undetected, while 35% of biopsies would have been avoided. Using PSA density combined with digital rectal examination instead of the free-to-total PSA ratio an identical number of cancers remained undetected with a similar decrease in biopsies.

Biopsy indication	*Biopsies / PC*	*(Mean ± SE) % biopsies less*	*(Mean ± SE) % PC lost*	*Biopsy/PC ratio*	*Pathologically confined/extensive ratio*
PSA 4-10 ng./ml.	427/99	---	---	5.1	---
Abnormal digital rectal examination	73/43	83 ± 1.8	57 ± 5.0	4.7	18 / 8
Free-to-total PSA ratio 0.2 or less	239/80	44 ± 2.4	19 ± 4.1	4.6	7 / 3
Abnormal digital reetal examination, free-to-total PSA ratio 0.2 or less	264/87	38 ± 2.3	12 ± 3.2	4.6	5 / 0
Abnormal digital rectal examination PSA density 0.12 ng./ml./cc or more	242/85	43 ± 2.3	14 ± 3.5	4.5	3 / 1
Total serum PSA greater than age speeifie referenee range, abnormal Digital reetal examination	301/81	30 ± 2.1	18 ± 3.8	5.0	1 / 2
Total serum PSA greater than age speeifie referenee range, free-to-total PSA ratio 0.2 or less, and ab-normal digital rectal examination	362/92	15 ± 1.7	6 ± 2.4	50	0 / 0

Table 3:
Simulation of biopsy indications and results in 427 men with a total PSA of 4.0 to 10.0 ng/ml. Of 101 men with prostate cancer 54 underwent radical prostatectomy, including 30 with stage pT2, 13 with stage pT3 and 6 with stage pT4 disease, and 5 in whom staging was not yet performed. The tumors were classified as histologically confined (stage pT2) or extensive (stage pT3).

The overall ratio of number of biopsies-to-number of carcinomas represents the effect of the stimulation on the entire population of 4,800 men with 977 biopsies, showing the possible gain of the application of additional screening modalities to the intermediate PSA range compared to the actual screening policy. To illustrate the effect of various cutoff levels of the free-to-total PSA ratio in combination with digital rectal examination for selection of men for biopsies in the intermediate PSA range, table 4 lists the sensitivity and specificity with the standard error for this combination of modalities. Table 5 shows the age and pathological tumor stage (when radical prostatectomy was performed) for men with cancers lost to detection in the case selection simulation by use of free-to-total PSA ratio combined with digital rectal examination, PSA density plus digital rectal examination and age specific reference ranges plus digital rectal examination for a PSA of 4.0 to 10.0 ng./ml.

Free-to-total PSA ratio cutoff	*% sensitivity*	*% specificity*
0.16	78	63
0.18	83	55
0.20	87	46
0.22	91	36

Table 4:
Sensitivity (standard error 1.4%) and specificity (standard error 2.1%) for various cutoff values of free-to-total PSA ratio as an indicator for biopsy with digital rectal examination for intermediate PSA of 4 to 10 ng./ml. in 427 men

	Free-to-total ratio		PSA Density		PSA age specific reference range	
Age (Years)	*Stage T2*	*Stage T3*	*Stage T2*	*Stage T3*	*Stage T2*	*Stage T3*
55-60	2	---	1	---	---	2
60-65	1	---	1*	---	1	---
65-70	1	---	---	---	---	---
70-75	1*	---	1	---	---*	---

* One cancer of unknown stage

Table 5:
Number and pathological stage of cancers lost to detection by use of digital rectal examination combined with free-to total PSA ratio, PSA density and age specific reference ranges for a PSA of 4.0 to 10.0 ng./ml.

Discussion

Since the initial reports concerning the free-to-total PSA ratio in 1991, improvement in specificity of total serum PSA to predict a positive prostate biopsy by use of the free-to-total PSA ratio has only been statistically significant in clinically select groups of patients but not in samples of the general population to which screening potentially will be applied. A previous study from our clinic concerning a screening population showed that free-to-total PSA ratio could decrease the number of biopsies by 35% at the cost of 11% fewer detected cancers [11]. The free-to-total PSA ratio in the intermediate PSA range or gray area of 4.0 to 10.0 ng./ml. significantly improved the discrimination of benign from malignant prostatic diseases compared to serum PSA only (fig. 3). A decreased number of false-positive indications for biopsy is important, particularly in the intermediate PSA range, since PSA values in men with benign conditions of the prostate, such as prostatitis or benign prostatic hyperplasia, overlap considerably those in men with a malignancy. In that range PSA adjusted values may be helpful, since almost half of the total number of biopsies (44% in our study) occur in that subgroup of participants (8% of our total population). Using age specific reference ranges for total PSA in addition to digital rectal examination in men with a PSA of 4.0 to 10.0 ng./ml. leads to a 30% decrease in biopsies, while 18% of the cancers remain undetected. These percentages compare unfavorably to the selection obtained by digital rectal examination combined with free-to-total PSA ratio or PSA density. Both regimens decrease the number of biopsies significantly more, while the number of undetected carcinomas remains similar. On the other hand, of all 3 modalities age specific PSA reference range is the most easily applied, followed by the free-to-total PSA ratio (particularly when the ProStatus-TM assay is used, which measures the total serum PSA and the free-to-total PSA ratio simultaneously). Calculation of PSA density requires transrectal ultrasonography volumetry, which is more time-consuming and more expensive. In this analysis 85% of carcinomas detected with PSA density were in individuals whose carcinomas were detected by the free-to-total PSA ratio, suggesting that the free-to-total PSA ratio measures the same biological entity as does PSA density. However, the correlation among the 3 modalities of free PSA, prostate volume and age is at best moderate (maximum correlation coefficient $r = 0.31$ [11]), and the metabolic pathway determining the free-to-total PSA ratio is still unknown.
Of equal importance as the number of undetected cancers are the characteristics of the detected and undetected carcinomas. In our study only limited information is given,

namely the age of the men with carcinomas that would remain undetected, and the pathological extent of those tumors that would contraindicate radical prostatectomy (table 5). In contrast to other reports [7], age specific PSA reference range does not mainly select younger men for prostate biopsies, since the distribution of undetected cancers is similar for all age groups, and not solely in the oldest men. Not detecting confined carcinomas might be regarded as favorable when they are of small volume and biologically insignificant. If they grow these cancers may be detected still at a confined stage during subsequent sereening. On the other hand, not detecting extensive carcinomas means missing larger cancers that are often beyond the scope of radical therapy, and that may present in a metastatic state during subsequent screening. A screening regimen that misses these larger tumors may be of limited value. Various characteristics of these screen detected tumors, such as tumor volume, grade and ploidy, are being studied in Rotterdam and will be reported separately. As long as the characteristics of screen detected cancers are not completely clear and the outcome has not been established by adequate followup, one can only conclude that in our study the various groups of men with cancers detected by each method of PSA adjustment do not completely overlap. In an effort to make the free-to-total PSA ratio even more specific, it has been suggested that the test be applied to younger men 55 to 65 years old and/or those with a smaller prostate. Free PSA showed a volume and age dependency [11]. Therefore, improved specificity of PSA not only by free PSA (free-to-total PSA ratio) but also by age and prostate volume might improve the specificity for prostate cancer. Previously, however, multivariate analysis showed that in the complete PSA range the power of prostate volume and age to predict a positive biopsy was slight and insignificant compared to that of the free-to-total PSA ratio. This finding is probably due to the mutual correlation. In our study the correlation between free-to-total PSA ratio and age (and also prostate volume, not shown) was noted in men with a PSA of 4 to 10 ng./ml. The information given by age and volume might be used in various ways, for example by construction of age specific reference ranges for free-to-total PSA ratio. This factor seems to be of little benefit when the lower 95th percentile of the free-to-total PSA ratio is equal among the various age groups (table 1).

The choice of the best cutoff value for free-to-total PSA ratio in the intermediate PSA range depends on a variety of arguments, which include mainly the combination of screening modalities used and the level of sensitivity. This choice is illustrated most easily by presenting the sensitivity and specificity for various levels between 0.16 and 0.22

ng./ml. (table 4). Although the free-to-total PSA ratio also increases the specificity of PSA at a PSA of 10 ng./ml. or more [15] the clinical usefulness is limited. At that range the ratio of number of biopsies-to-number of carcinomas is less than 2, which makes it acceptable to perform biopsy in all men with high PSA levels. For similar ethical reasons it is difficult to extend the biopsy indication to all men with PSA ranges of less than 4.0 ng./ml., although the number of carcinomas found will be increased. It must be realized that a biopsy indication for the free-to-total PSA ratio of 0.20 or less at a PSA of 2.0 to 4.0 ng./ml. will increase the number of biopsies by approximately 60% [11]. The biopsy rate per cancer found may increase to 6.3%.

Conclusions

In the intermediate PSA range of 4.0 to 10.0 ng./ml. the free-to-total PSA ratio improves the specificity of total serum PSA significantly. In populations of symptomatic men who present to a urological clinic the amount of improvement may be different. A cutoff level of 0.20 or less combined with a positive digital rectal examination as indicators for biopsy decreases the number of biopsies in that range by 38%, while maintaining the level of sensitivity at 88%. The undetected carcinomas are likely to be organ confined. The effect on the numbers of biopsies needed to detect 1 carcinoma in the entire population is limited, changing the ratio of number of biopsies-to-number of carcinomas from 5.1 to 4.6. Use of the free-to-total PSA ratio may be more cost-effective than the time-consuming measurement of PSA density, while the same number of men is selected for biopsies. Biopsy policies may be constructed using optimal cutoffvalues of parameters (free-to-total PSA ratio, PSA age specific reference ranges and PSA density) in addition to total PSA and digital rectal examination.

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Chapter IV

Comparison of PSA corrected for total prostate volume and transition zone volume in a population based screening study*.

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Abstract

The objective of this study is to compare the discriminatory potential between prostate cancer and benign conditions of the prostate in a population-based screening study, of serum prostate specific antigen levels (PSA) and PSA corrected for both the total prostate volume (PSA-D) and the transition zone volume (PSA-T).
Methods: In a randomized population based screening study (Rotterdam section of the European Randomized Study of Screening for Prostate Cancer) in which 10,865 men have been screened, the results of 1,202 biopsied men with PSA levels of 4 ng./ml. or more were evaluated. Planimetric and prolate ellipsoid volume of the total prostate as well as of the transition zone were measured. The measured volumes were compared with the volumes of 57 radical prostatectomy specimens through Spearmans correlation and agreement tests. A receiver operator characteristics (ROC) curve analysis was done of sensitivity and specificity of biopsy indications through PSA and PSA corrected for the volumes measured with transrectal ultrasound.
Results: In the 1,202 biopsied men, 361 cases of prostate cancer were diagnosed. Both PSA-D and PSA-T showed a significantly higher area under the ROC curve (respectively 0.77 and 0.79) than PSA alone (area: 0.65)
There was no significant difference between PSA-D and PSA-T. The use of a PSA-D threshold value of 0.10 ng./ml./cc would have avoided 28% of biopsies at the cost of 10% of detectable cancers. A PSA-D threshold of 0.15 ng./ml./cc would have saved 73.8% of biopsies at the cost of not diagnosing 43.8% of detectable cancers.

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* *Comparison of PSA corrected for total prostate volume and transition zone volume in a population based screening study. JBW Rietbergen, R Kranse, RF Hoedemaeker, AE Boeken Kruger, ChH Bangma, WJ Kirkels, FH Schröder.* UROLOGY *1998; vol 52: 237-246.*

Conclusions: The planimetrically obtained prostate volume showed a more favorable agreement with the radical prostatectomy volume than the prolate ellipsoid volume. The discriminatory potential of the corrected PSA value is better in predicting the results of needle biopsy of the prostate when compared to PSA alone. The use of the transition zone volume for this correction results in a higher discriminatory potential when compared to the use of the total prostate volume; however, the observed difference was not statistically significant.

Introduction

PSA is an important but imperfect means of detecting prostate cancer. A cutoff value between 3 and 4 ng./ml. is generally used as a biopsy indication [1-4]. Approximately 80% of all cancers detected in these programs are detected in the PSA range above the cutoff, the cancers below the cutoff are detected by digital rectal examination (DRE) and/or transrectal ultrasonography (TRUS). Unfortunately the performance of PSA is poor in terms of discriminating between benign and malignant biopsy results since several conditions such as benign prostate hyperplasia (BPH) [5], acute prostatitis [6], prostatic ischemia [7] and other forms of perturbation may increase the serum PSA level. This results in a large number of false positive biopsy indications. Means of improving the specificity and reducing the false positive biopsy indications are under discussion. Babaian et al. showed a direct relationship between prostate gland volume and the serum PSA value as well as a cancer value threshold [8,9]. Benson et al. further elaborated this concept by introduction of PSA-density (PSA-D). They showed that PSA-D discriminates better between patients with prostate cancer and BPH than PSA alone [10]. Several authors concluded that the use of PSA-D can safely reduce the number of patients subjected to systematic biopsies without significantly compromising cancer detection in populations of referred patients [11,12]. Littrup et al. plead for the application of optimized decision levels i.e. performance of biopsy if the PSA-D level is above the threshold level or the findings at digital rectal examination are abnormal [13]. These statements however, were opposed by several other authors. Brawer et al. did not observe an advantageous effect of the use of PSA corrected for prostate volume in 218 referred patients [14]. Others observed a positive effect but concluded that over 30% to 50% of cancers would not have been detected if the often recommended PSA-D threshold value of 0.15 ng./ml./cc had been used [15-17].

The observation that serum PSA is more strongly correlated with the volume of epithelium in the transition zone [18] has led to the evaluation of PSA corrected for transition zone volume (PSA-T). Two retrospective referred patient based studies concluded that PSA-T is more accurate in predicting a positive biopsy than is PSA-D for PSA levels between 4.1 ng./ml. and 10 ng./ml. [19,20]. However, Gohji et al found no advantage of the use of PSA-T over PSA-D in a population of 287 Japanese men [21]. In a retrospective evaluation of the pilot studies of the ERSPC section Rotterdam, a modest but statistically insignificant improvement of PSA-T over PSA-D was found. This evaluation was done on 1726 screened men, of whom 308 were biopsied which resulted in the detection of 67 cases of prostate cancer [22]. The majority (two thirds) of these men however, were not included in the current evaluation.
In this paper we assessed the value of PSA corrected for total prostate volume and transition zone volume in 1202 consecutively biopsied men with PSA levels greater than or equal to 4 ng./ml. in a population based screening study. Furthermore, the methods of volume determination used for the PSA correction are evaluated.

Methods

Patients:
Between November 1993 and June 1997, 23,218 men between 54 and 76 years old responded to a letter of invitation to enter the European Randomized Study of Screening for Prostate Cancer (Section Rotterdam). The response rate was 42%. The only exclusion criterion was a previous diagnosis of prostate cancer. Written informed consent was obtained from all study subjects. Those who were included were randomized to either the screening arm or the control arm of the study. The men in the control arm were not offered testing in any way.
Of the 11,596 men in the screening arm 10,865 men underwent a serum PSA determination. The remaining 731 men were scheduled for the first screening visit in which bloodsamples will be drawn. One thousand three hundred and sixty-eight men had PSA levels greater than 3.9 ng./ml. (12.6 %). In the 1,239 biopsies that were performed, 373 cases of prostate cancer were detected (30.1%) and one case of leiomyosarcoma.

Techniques:

All 10,865 men underwent determination of serum PSA concentration (Hybritech Tandem-E PSA immunoenzymetric assay, Hybritech, Inc., San Diego, Calif), digital rectal examination (DRE) and trans-rectal ultrasonography (TRUS).

Blood samples were drawn before the other tests were performed. The cut-off level of the PSA test was set at 4.0 ng./ml., any value greater than 3.9 ng./ml. is considered elevated. At the time of screening the members of the screening team were unaware of the PSA results.

Digital rectal examination was performed by a resident urologist or an ultrasound technician; nodularity, induration and asymmetry were considered abnormal.

Biplanar TRUS was performed by a resident urologist or an ultrasound technician, using a Bruel & Kjaer® model 1846 mainframe and a 7 MHz biplanar endorectal transducer (B&K Medical Systems, Marlborough, MA), with the subject in the left lateral decubitus position. The sonographic criteria for prostate cancer described by Lee et al. were used [23]. All prostate biopsies were done by resident urologists (JBWR, AEBK and CHB) with ultrasound guidance, using a Manan pro-mag® 2.2 biopsy gun and an 18 gauge Bard® biopsy needle. All men with a PSA level higher than the threshold level were biopsied. If the biopsy indication was an elevated PSA level or an abnormal digital rectal examination, systematic sextant biopsies were performed. In case of a hypoechoic lesion, the lesion was sampled in addition to the sextant biopsy. All subjects received antimicrobial prophylaxis (Co-trimoxazole 960 mg p.o.) two hours prior and 4 hours after the procedure.

The pathological findings from sextant and ultrasound guided biopsies were the reference test for determining the presence or absence of prostate cancer.

Volume measurement and PSA corrected for prostate volume:

In all subjects the prostate volume was obtained through a planimetric volume measurement with a 0.5 cm step section. Both the transition zone volume and the total prostate volume were measured.

Furthermore the length, height and width of both transition zone and the total prostate were measured. These are respectively the cephalad-caudad, anteroposterior and transverse dimensions of the prostate. The length of the total prostate was obtained at the largest cephalad-caudad distance in the longitudinal plane. Reference points for the measurement of the length of the transition zone are the inner portion of the capsule and

the verumontanum. Land marks for the measurement of the width and height in the transverse plane, are the capsule and the distinct layer of fibrous tissue separating the transition zone from the central and periferal zone. The results were entered in the formula: 0.52*Length*height*width, to obtain the prolate ellipsoid volume.
The PSA density was determined through the quotient of the PSA value and the volume of the prostate. Four different indices are calculated:

PSA-D plan : (PSA / planimetrically measured total prostate volume);
PSA-T plan : (PSA / planimetrically measured transition zone volume);
PSA-D lwh : (PSA / prolate ellipsoid total prostate volume);
PSA-T lwh : (PSA / prolate ellipsoid transition zone volume).

Radical prostatectomy volume:
The prostate volume of the radical prostatectomy specimen of 57 men of the screening population under study treated in our institution was measured. After fixation the radical prostatectomy specimens were inked and step-sectioned at 4 mm intervals. Of each slice a H&E stained histological slide was prepared. Slide surface areas were measured by a digital morphometric analysis (Kontron imaging system (KS400), Kontron electronik GmbH, Eching, Germany). The total prostate volume was determined by totaling all areas and multiplying them by 4mm.

Statistical analysis:
The Mann-Whitney U test is a nonparametric equivalent to the t-test and uses the null-hypothesis that two independent samples come from populations with the same distribution. The observations from both groups are combined and ranked, with the average rank assigned in the case of ties. The P value represents the chance that the null hypothesis is rejected wrongly. This test was used to assess differences in PSA values, PSA values corrected for volume and prostate volume and in men with benign and malignant biopsy results (Table 1).
Spearmans correlation was used to determine the relationship between total gland volume and transition zone volume (Fig. 4) and the relationship between the prostate volume obtained by TRUS volume measurement and the volume of the radical prostatectomy specimen (Fig. 1). Spearman's rho measures the association between rank orders. Correlation coefficients range in value from –1 (a perfect negative relationship) and +1 (a perfect positive relationship).

Agreement between the applied volume measurements was analyzed through the method of Bland and Altman [24]. Because of increasing variation in the high volume ranges a logarhitmic transformation was used as described by Hollis [25]. To prove or refute agreement between two methods the mean value of the methods is plotted against the difference. If two methods are to agree the points on a scatterplot of the two methods must lie close to the line of equality over the total range. Systematic over- or under-estimation of one of the methods leads to a horizontal line above or under the X-axis. A visible trend indicates that the difference of the two methods varies over the range of the mean. In our evaluation a line was fitted through the data to visualize a possible trend. The limits of agreement are given by the mean $\pm$ 2 * Standard Deviation. The closer these limits are to the mean, the better the agreement.

The discriminatory potential between benign and malignant biopsy results of PSA and volume-corrected PSA values were assessed using Receiver Operating Characteristics (ROC) curves. These illustrate the reciprocal relationship between sensitivity and specificity by plotting false positive (one minus specificity) versus true positive (sensitivity). The larger the area under the curve i.e. the closer the curve is to the upper left corner of the graph, the better the performance of the test. Statistical significance of differences in the area under different curves was calculated with the method as described by Hanley and McNeil [26]. Since the data to be compared are derived from the same cases, the biopsied population of 1202 men was divided into two populations by randomization, to correct for possible correlations induced by the paired nature of the data. This randomization has led to 613 men in the first population (1) and 589 men in the second population (2). The statistical significance of the difference in area under the curve of two tests was determined by comparing the test results in the first population with the test results in the second population.

Results

Population:

A total of 10,865 men were screened in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). In 2,619 of these men a biopsy was indicated by either abnormal DRE and/or TRUS findings or a serum PSA level of 4 ng./ml. or higher. Systematic sextant biopsies were performed in 2,365 of these men. Two hundred and fifty-four men were not biopsied for various reasons or biopsy results are pending. In these biopsied men 505 cases of prostate cancer and one case of leiomyosarcoma were detected resulting in an overall detection rate of 4.7%. In this evaluation only men with PSA levels of 4 ng./ml. or higher were included since all men were biopsied above the PSA threshold of 4 ng./ml. to determine the presence or absence of prostate cancer. 1,368 (12.6%) of all screened men had a PSA level of 4 ng./ml. or greater. A biopsy was performed in 1,239 men and 373 (30.2%) cases of prostate cancer were diagnosed. Reasons for not performing a biopsy were: Refusal of biopsy or withdrawal from study: 80; Anticoagulant medication : 20; Pending biopsy result : 29.

In 1202 men all data concerning biopsy results and volume measurements were complete. All evaluations were done on these 1202 men in whom 361 (30%) cases of prostate cancer were detected.

Of these 1202 men, 724 men had normal DRE and TRUS findings. Within this subset 127 cases (34%) of stage T1C prostate cancer were detected.

The distributions of PSA, PSA-D, PSA-T, total prostate volume and transition zone volume are shown in table 1. This was done for all 1202 men under study, as well as for those with prostate cancer and those with a benign biopsy result. The difference between benign and malignant cases was statistically significant for all parameters ($p<0.001$, Mann-Whitney U).

	PSA (ng./ml.)	PSA-D (ng./ml./cc)	PSA-T (ng./ml./cc)	Total prostate volume (cc)	Transition zone volume (cc)
	All (N=1202)				
Mean	8.9	0.2	0.38	51.7	31.9
Standard error	0.49	0.01	0.023	0.7	0.6
Median	5.8	0.13	0.23	46.1	26.4
Range	4.0 – 315.7	0.03 – 7.6	0.04 – 15.2	15.4 – 224.6	5.5 – 166.7
	Benign (N=841)				
Mean	6.7	0.13	0.23	55.9	35.6
Standard error	0.13	0.0026	0.0056	0.9	0.7
Median	5.5	0.12	0.195	49.9	30.4
Range	4 – 49.4	0.027 – 0.92	0.04 – 1.9	18.9 – 224.6	6.0 – 166.7
	Prostate cancer (N=361)				
Mean	14.0	0.36	0.72	41.7	23.5
Standard error	1.6	0.036	0.072	0.94	0.77
Median	6.9	0.20	0.42	36.1	18.9
Range	4.0 – 315.7	0.04 – 7.6	0.06 – 15.2	15.4 – 108.5	5.5 – 84.9
P value (Mann-Whitney U test) benign versus prostate cancer	P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001

Table 1:
Distribution of PSA, PSA-D, PSA-T, total prostate volume and transition zone volume for the total study population, those with a benign biopsy result and those with prostate cancer.

Comparison of radical prostatectomy volume and TRUS measured volume.

Of fifty-seven of these men, treated by radical prostatectomy in our institution, the volumes of the radical prostatectomy specimen were compared to the results of planimetric and prolate ellipsoid volume measurements by TRUS. The mean volume of the radical prostatectomy specimen is 34.1 cc, the median is 27.8 cc (range 16.8 – 73.3). The mean planimetric volume measured by TRUS of these 57 cases is 42.1cc, the median is 35.4 cc (range 21.4 – 99.7). The mean prolate ellipsoid volume measured by TRUS of these 57 cases is 41.3 cc, the median is 35.6 cc (range 16.4 – 103.7). In figure1 the volumes measured by TRUS are plotted versus the radical prostatectomy volume. The Spearman rank correlation coefficient was determined for both plots. For the planimetric volume (fig. 1A) r = 0.81 ($p<0.0001$). For the prolate ellipsoid volume (fig. 1B) r = 0.83 ($p<0.0001$).

Figure 2 shows the agreement evaluation. In figure 2A the mean value of the log radical prostatectomy volume and the log planimetric volume obtained by TRUS is plotted versus the difference (log planimetric volume measured by TRUS minus log radical prostatectomy volume). The mean value is 0.092 (standard error of the mean : 0.012). The mean value plus or minus two standard errors of the mean does not include zero and remains positive. This indicates that the planimetric volume systematically overestimates the radical prostatectomy volume. The line fitted through the data is described by the formula: $y = 0.12 + ax$ in which $a = -0.015$. The 95% confidence limits of **a** are -0.13 and 0.36. This confidence interval includes zero. This indicates that the data show no significant trend and the observed difference between the measured volume and the radical prostatectomy volume does not depend on the average value of the two volumes compared. Specifically, the planimetric volume measurement systematically overestimates the volume of the radical prostatectomy specimen. The limits of agreement are described by the mean plus or minus two standard deviations. For the log planimetric volume minus the log radical prostatectomy volume this is 0.092 ± 0.188. The back transformation of this logarithm shows that the mean planimetric volume overestimates the radical prostatectomy volume by 23% and the radical prostatectomy volume differs from the planimetric volume measurement by 43% below and 67% above.

In figure 2B the mean value of the log radical prostatectomy volume and the log prolate ellipsoid volume obtained by TRUS is plotted versus the difference (log prolate ellipsoid volume measured by TRUS minus log radical prostatectomy volume). The mean value is –0.072 (standard error of the mean : 0.014). The mean value plus or minus two standard errors of the mean does not include zero and remains negative. The prolate ellipsoid volume systematically underestimates the radical prostatectomy volume. The line fitted through the data is described by the formula: $y = 0.19 + ax$, in which $a = -0.17$. The 95% confidence limits of **a** are -0.32 and -0.012. This confidence interval does not include zero. This indicates that the data show a significant trend because the observed difference between the two volumes depends on the average value of the two compared volumes. The limits of agreement for the prolate ellipsoid volume minus the log radical prostatectomy volume are -0.072 ± 0.208. The back transformation of this logarithm shows that the mean prolate ellipsoid volume underestimates the radical prostatectomy volume by 15% and the radical prostatectomy volume differs from the prolate ellipsoid volume measurement by 31% below and 53% above.

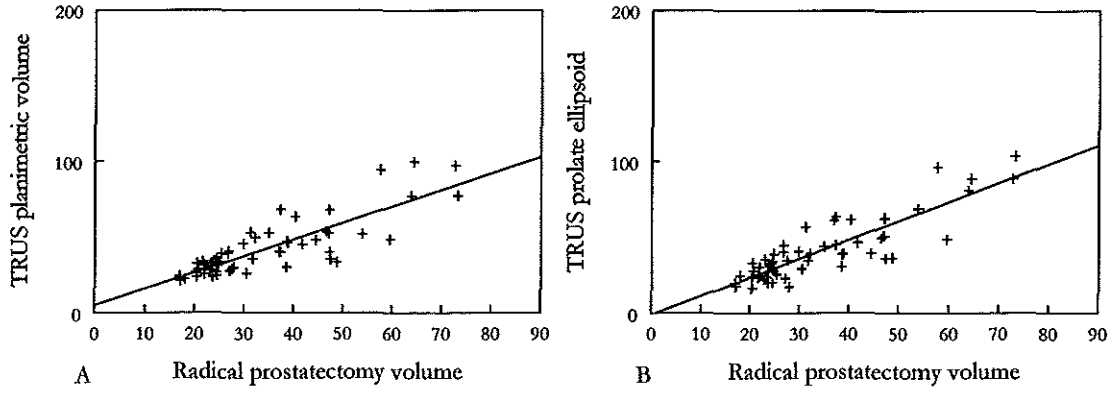

Figure 1:

Radical prostatectomy volume versus A: planimetric volume measured by TRUS (correlation coëfficient: r = 0.81). B: prolate ellipsoid volume measured by TRUS (correlation coëfficient: r = 0.83)

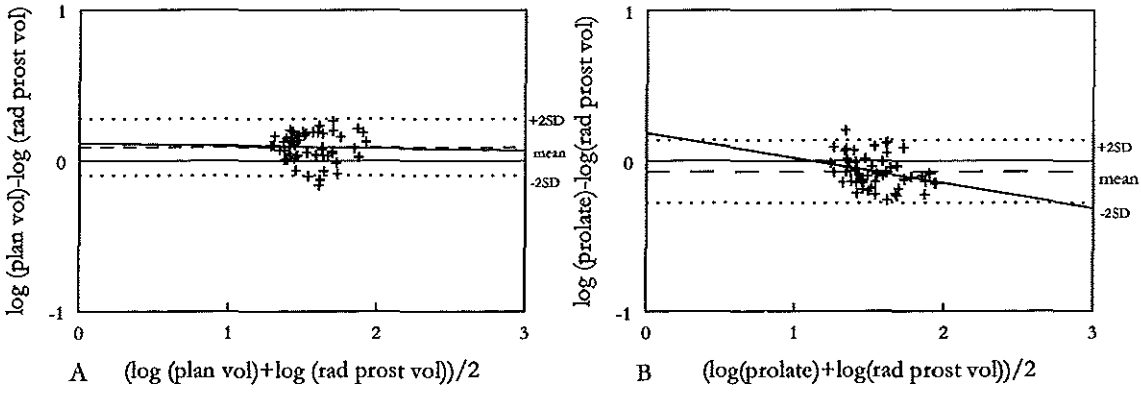

Figure 2:

Agreement plot: A: Mean of the log planimetric volume measured by TRUS and the log radical prostatectomy volume versus the difference of the log planimetric volume and and the log radical prostatectomy volume. B: Mean of the log prolate ellipsoid volume measured by TRUS and the log radical prostatectomy volume versus the difference of the log prolate ellipsoid volume and and the log radical prostatectomy volume.

Comparison of PSA-D and PSA-T by planimetric and prolate ellipsoid volume.

The agreement plot in Figure 3A shows the mean value of log (PSA-D-plan) and log (PSA-D-hwl) versus the difference of log (PSA-D plan) and log (PSA-D hwl). The mean value is –0.025 (standard error of the mean: 0.0023). The line fitted through the data is described by the formula: y= -0.03 + ax in which a= -0.009. The 95% confidence limits of a are –0.03 to 0.007.

The second agreement plot (figure 3B) shows the mean value of log (PSA-T-plan) and log (PSA-T-hwl) versus the difference of log (PSA-T plan) and log (PSA-T hwl). The mean value is –0.074 (standard error of the mean: 0.003). The line fitted through the data is described by the formula: y= -0.08 + ax in which a= -0.014. The 95% confidence limits of a are –0.03 to 0.004.

In both agreement plots the 95% confidence interval of a includes zero. However, the standard error of the mean does not include zero, thus there is a systematic bias, i.e. there is a constant difference in outcome between the PSA value corrected for the planimetric volume and the PSA value corrected for the prolate ellipsoid volume, which is independent of the size of the prostate.

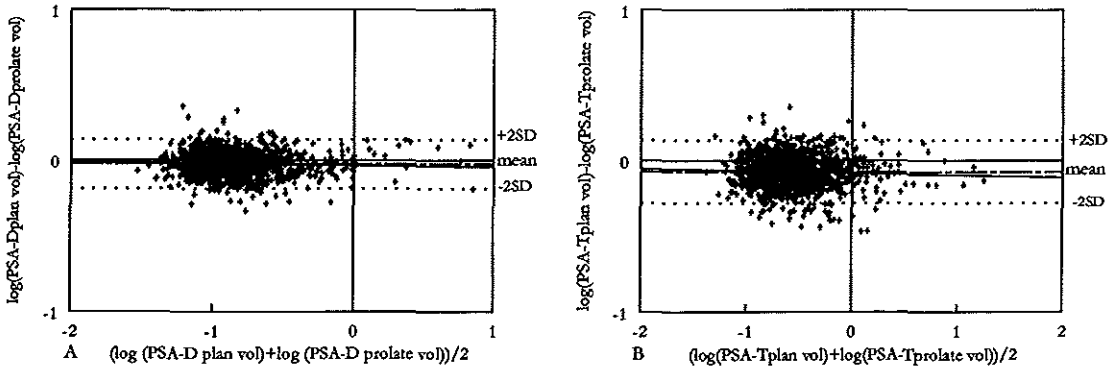

Figure 3:

Agreement plot for PSA corrected for volume: Mean of the log planimetric volume measured by TRUS and the log prolate ellipsoid colume measured by TRUS versus the difference of the log planimetric volume and and log prolate ellipsoid colume measured by TRUS for A: Total prostate volume and B: Transition zone volume.

Comparison of total prostate volume and transition zone volume:

In a scatter plot (figure 4) the planimetric total prostate volumes were plotted versus the planimetric transition zone volumes. The mean planimetric total prostate volume measured by TRUS is 51.7cc, the median is 46.1 cc (range 15.4 – 224.6). The mean planimetric transition zone volume is 31.9 cc, the median is 26.4 cc (range 5.5 – 166.7). The Spearman correlation coefficient for total prostate volume versus transition zone volume is 0.95 rho ($p<0.0001$).

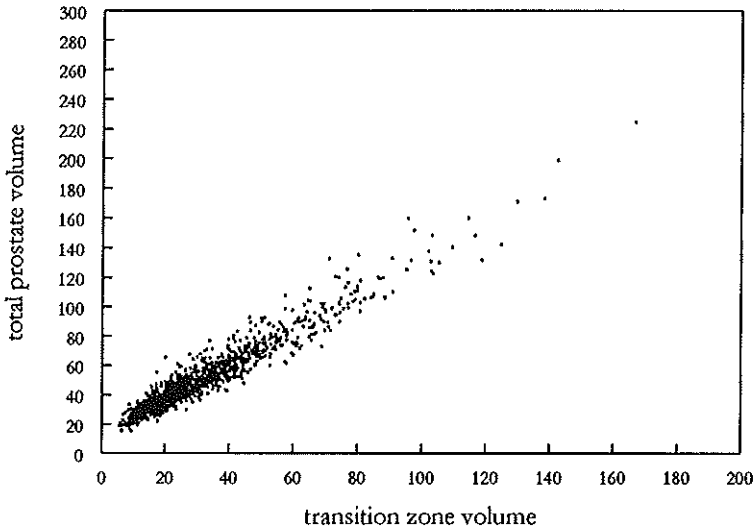

Figure 4:

Total prostate volume versus transitionzone volume.

Receiver operating characteristic curves:

Assessment of sensitivity and 1-specificity was done through ROC curve analysis for five modalities, PSA only; PSA-D-plan; PSA-D-lwh; PSA-T-plan and PSA-T-lwh. The areas under the curve are shown in table 2, for all biopsied men and for those with normal DRE and TRUS findings. The differences between the area under the curve of PSA only and all four PSA density methods were statistically significant ($P<0.0001$). The differences in area under the curve between the volume corrected PSA values were not statistically significant. This is further specified in table 3. Furthermore the comparable volume corrected PSA values in the two populations obtained through randomization showed no statistically significant differences.

	Area all biopsied	*Area normal DRE and TRUS*
PSA only	0.65	0.61
PSA-D-plan	0.77	0.71
PSA-D-lwh	0.76	0.69
PSA-T-plan	0.79	0.72
PSA-T-lwh	0.78	0.70

Table 2.
Area under the ROC curve for PSA and PSA corrected for volume for all men biopsied and men with normal DRE and TRUS findings.

	PSA only (1)	PSA-D-plan (1)	PSA-D-lwh (1)	PSA-T-plan (1)	PSA-T-lwh (1)
PSA only (2)	0.41	<0.001	<0.001	<0.001	<0.001
PSA-D-plan (2)	<0.001	0.33	0.25	0.44	0.33
PSA-D-lwh (2)	<0.001	0.47	0.37	0.43	0.45
PSA-T-plan (2)	<0.001	0.20	0.14	0.28	0.19
PSA-T-lwh (2)	<0.001	0.20	0.14	0.28	0.19

Table 3.
P values for significance in difference in area under the various ROC curves in population 1: (1) and population 2: (2).

The ROC curves for PSA only and PSA-D-plan and PSA-T-plan are shown in figure 5. The respective areas under the curves are 0.65 for PSA only, 0.77 for PSA-D and 0.79 for PSA-T. A similar evaluation was done for men with a prostate volume greater than 40 cc and men with a prostate volume of 40 cc or less. In both groups no significant difference was found in area under the ROC curve of PSA-D and PSA-T.

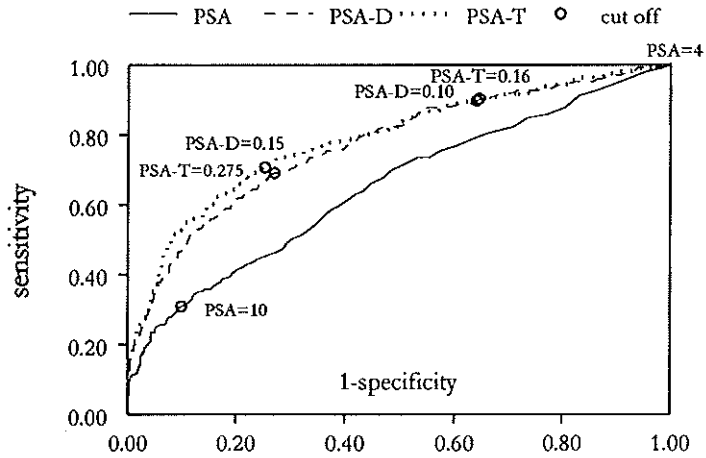

Figure 5:
Receiver operating characteristics curves for PSA; PSA-D and PSA-T. Various cutoff levels for all parameters are specified.

Impact on cancer detection:

The consequences for prostate cancer detection and the number of biopsies are shown for the use of PSA-D and PSA-T in table 4. The cutoff values were chosen based on the available literature. The PSA volume quotients are based on the planimetrical volume. For PSA-D the values reported in literature are 0.10 ng./ml./cc; 0.12 ng./ml./cc and 0.15 ng./ml./cc. and for PSA-T 0.35 ng./ml./cc and 0.45 ng./ml./cc. The additional cutoffs were chosen to establish a match in the number of biopsies avoided with application of the PSA corrected for volume in order to compare the number of cancers not diagnosed at comparable numbers of biopsies avoided. If biopsies would have been performed above a PSA-D cutoff of 0.15 ng./ml./cc, 60.1% of biopsies would have been avoided and 30.7% of cancers would not have been diagnosed. At a PSA-T cutoff of 0.275 ng./ml./cc, 60.3% of biopsies would have been avoided and 28.5% of cancers would have been missed.

The same was done in table 5, for the scenario where the PSA-D or PSA-T is only used for prostates with elevated PSA levels and normal DRE and TRUS findings.

N=1202	*Biopies avoided*	*%*	*PC not diagnosed*	*%*
PSA-D ≥ 0.10	337	(28.0%)	37	(10.2%)
PSA-D ≥ 0.12	505	(42.0%)	64	(17.7%)
PSA-D ≥ 0.15	722	(60.1%)	111	(30.7%)
PSA-D ≥ 0.185	887	(73.8%)	158	(43.8%)
PSA-D ≥ 0.22	978	(81.4%)	206	(57.1%)
PSA-T ≥ 0.16	331	(27.5%)	35	(9.7%)
PSA-T ≥ 0.20	503	(41.8%)	67	(18.6%)
PSA-T ≥ 0.275	725	(60.3%)	103	(28.5%)
PSA-T ≥ 0.35	876	(72.9%)	153	(42.4%)
PSA-T ≥ 0.45	981	(81.6%)	197	(54.6%)

Table 4.
Percentage biopsies avoided and cancers not diagnosed at various PSA-D and PSA-T levels.

N=1202	*Biopsies avoided*	*%*	*PC not diagnosed*	*%*
PSA-D ≥ 0.10	235	(19.6%)	18	(5.0%)
PSA-D ≥ 0.12	344	(28.6%)	31	(8.6%)
PSA-D ≥ 0.15	489	(40.7%)	51	(14.1%)
PSA-D ≥ 0.185	518	(43.1%)	54	(15.0%)
PSA-D ≥ 0.22	640	(53.2%)	86	(23.8%)
PSA-T ≥ 0.16	240	(20.0%)	21	(5.8%)
PSA-T ≥ 0.20	354	(29.5%)	34	(9.4%)
PSA-T ≥ 0.275	508	(42.3%)	51	(14.1%)
PSA-T ≥ 0.35	592	(49.3%)	69	(19.1%)
PSA-T ≥ 0.45	645	(53.7%)	84	(23.3%)

Table 5.
Percentage biopsies avoided and cancers not diagnosed at various PSA-D and PSA-T levels if PSA-D or PSA-T threshold levels are only applied to men with elevated PSA levels and normal DRE and TRUS findings.

Discussion

PSA-D has been proposed as an effective means of discriminating between elevated PSA as a result of benign and malignant prostatic disease [10-13]. However, this method has also been criticized because of its lack of sensitivity [16]. Others concluded that PSA-D did not enhance the ability of serum PSA alone to predict the presence of prostate cancer [14]. A partial explanation for this according to Catalona et al. is that the relationship between transrectal ultrasound volume and pathological prostate weight is not great (r = 0.61). This might very well be caused by subjectivity involved in measuring the TRUS volume. However, even if the actual pathological gland volume would have been used in the determination of PSA-D, a PSA-D value greater than 0.10 ng./ml./cc would have missed 29% of cancers [16].

To assess the correlation between the prostate volume at radical prostatectomy and the volume measured by TRUS we compared the volumes of 57 radical prostatectomy specimens with the prolate ellipsoid and planimetric volumes that were measured at the time of screening. We found correlations of 0.81 and 0.83 respectively (Fig 1). This strong correlation however, does not imply that the two volumes agree since correlation only means that the points in the scatterplot lie along any straight line. Agreement means that these points lie along the line of equality. As can be observed from Fig. 2 the planimetric volume and the radical prostatectomy volume agree well. The systematic bias allows the use of a PSA volume quotient since it only influences the cutoff value.

Although the correlation coefficient of the prolate ellipsoid volume and the radical prostatectomy volume is slightly higher than in the comparison with the planimetric volume, the agreement is poor. The line fitted through the data shows a significant trend which indicates that with an increasing mean value of the measurement there is also an increasing difference between the prolate ellipsoid volume and the radical prostatectomy volume. Whether the limits of agreement are acceptable is a matter of clinical judgement, unfortunately there are no statistical answers to this question. The major observation based on the agreement plot is that the limits of agreement of the planimetric volume measurements are closer to the mean and show no significant trend in contrast to the prolate ellipsoid volume. This implies that the data obtained through planimetric measurement are more reliable. This is in line with the results of previous evaluations of the pilot study of the ERSPC [27] and the observations by Littrup et al. [28]. However, no agreement plots were used to show this reliability.

The use of PSA-T is still controversial. Only few publications are available. The fact that the transition zone is most strongly correlated with the PSA level has led to assessment of the PSA-T. Kalish et al. and Zlotta et al. [19,20] report a higher sensitivity and specificity for PSA-T when compared to PSA-D. In the first mentioned paper the contrast may be enhanced by the striking poor performance of PSA-D in the population under study. Both studies were done on a limited number, respectively 59 and 162, referred men, whereas our results are based on a large cohort of healthy participants in a population based screening study. Their findings were in line with those of Kurita et al [29]. They performed a ROC curve analysis on 164 men (44 cases of prostate cancer). The area under the curve was 0.667 for PSA alone, 0.663 for PSA-D and 0.826 for PSA-T which was significantly different from PSA alone and PSA-D. In an other report also on Japanese men, it was concluded that PSA-D offers additional information in men with intermediate PSA concentrations but PSA-T does not [21]. In our series the values for PSA-D and PSA-T were calculated using both planimetric and prolate ellipsoid volume. The agreement between the two methods is shown in Fig. 3, for the total prostate volume and the transition zone volume. It can be appreciated that both methods agree well. The limits of agreement however, are more favorable for the use of total prostate volume when compared to the use of transition zone volume. It has been recognized that the accuracy of the transition zone measurement is ultrasonographer dependent which may influence the reproducibility of PSA-T.

We compared the correlation between the total prostate volume and the transition volume (Fig.4). The correlation coefficient was 0.95. Based on this finding it is not to be expected that PSA-T would be of more value than PSA-D in increasing the performance of the screening procedure. This was confirmed by the ROC curve analysis. The area under the curve for PSA alone is 0.65 which is comparable to the findings of Kurita et al.. However, the curves for PSA-D and PSA-T showed a strong overlap (Fig.5) specially in the area of interest i.e. the area where a potential cutoff value for PSA-D and PSA-T is expected. The area under the curve is 0.77 for PSA-D and 0.79 for PSA-T. This small difference however, is not significant (p= 0.44). Evaluation of PSA-D and PSA-T in men with prostate volumes higher than 40 cc and men with a prostate volume of 40 cc or lower showed identical results. The only significant difference was that between PSA and PSA corrected for either transition zone or total prostate volume. The differences in area under the curve between PSA corrected for prolate ellipsoid volume and planimetric volume showed a trend in favor of the planimetric volume measurement but this difference was not significant as is shown in table 3.

Assessment of the number of biopsies avoided and prostate cancers not diagnosed shows that there is no advantage if PSA-T is used instead of PSA-D. The number of biopsies performed and cancers not diagnosed compare favorably. If a PSA-D cutoff of 0.10 ng./ml./cc would have been used in our series, 28% of biopsies would have been avoided at the cost of 10.2% of cancers remaining undetected. In the series of Catalona et al the use of the same cutoff would have saved 42.2% of biopsies, at the cost of 29% of cancers. To save 42% of biopsies in our series we would have had to use a PSA-D cutoff of 0.12 ng./ml./cc. Seventeen percent of cancers would have been missed. These differences however might be based on differences in population and the type of measurement since we used the planimetrically determined volume whereas Catalona et al used the prolate ellipsoid volume. Application of PSA corrected for volume exclusively on patients with normal DRE and TRUS findings would only give a marginal improvement of the number of cancers missed. If a PSA-D threshold of 0.15 ng./ml./cc is used, 41% of biopsies will be avoided at the cost of 14% of cancers that remain undetected.

Conclusion

Both the planimetric and prolate ellipsoid method of volume measurement show a favorable correlation to the radical prostatectomy volume. The agreement of the planimetric measurement however, is slightly better. By contrast this method is more time consuming than the prolate ellipsoid method. We found no significant difference in the ROC curve analysis between PSA corrected for planimetrically determined volume and prolate ellipsoid volume.

The results show that if PSA is corrected for prostate volume there is an increase in specificity but a decrease in sensitivity is inevitable. The area under the ROC curve was slightly higher for PSA-T than for PSA-D (0.79 versus 0.77); this difference, however, was not statistically significant. Thus, although the use of of PSA-T results in a higher discriminatory potential between prostate cancer and benign conditions of the prostate, it does not do so significantly and not in the area of interest when compared to the use of PSA-D within a screening population. However, both methods improve the performance of PSA as a screening test significantly. The use of a PSA-D or PSA-T cutoff value depends fully on the number of prostate cancers that is "affordable" to miss. Unfortunately the answer to this question can only be given when proof concerning the benefit of prostate cancer screening is available.

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Part B

The Biopsy procedure

Chapter V

Complications of transrectal ultrasound (trus) guided systematic sextant biopsies of the prostate: Evaluation of complication rates and risk factors within a population based screening program*.

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Abstract

Screening for prostate cancer with the purpose to reduce the mortality and morbidity from this disease has become an important issue in recent years. Of all diagnostic procedures used to diagnose prostate cancer, biopsy of the prostate is the cause of most complications. To evaluate the safety of the screening procedure we have evaluated the complications and risk factors for complications within the screened population of the European Randomized Study of Screening for Prostate Cancer (ERSPC) section Rotterdam.

Material and methods: Between June 1994 and July 1996 1,687 TRUS guided systematic sextant biopsies were performed after screening of 6,198 men through PSA, digital rectal examination and transrectal ultrasonography.

Results: With these 1,687 biopsies, 302 cases of prostate cancer were diagnosed. Mild complications as haematuria and haematospermia were reported frequently with rates of 23.6 and 45.4%. More severe complications were far less frequently seen. Fever, usually of low grade, was seen after 4.2% of biopsies. Seven men (0.4%) were admitted to a hospital after biopsy. Risk factors for complications could not be identified.

Conclusion: Review of literature concerning transrectal biopsies of the prostate shows that the complication rates within this screened population are comparable to those reported within referred patients. The admittance rate is slightly lower. TRUS guided systematic sextant biopsy of the prostate is a safe procedure for the diagnosis of prostate cancer within the general population, however, identification of risk factors for complications might further improve the safety of the screening procedure.

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* *Complications of transrectal ultrasound guided systematic sextant biopsies of the prostate: evaluation of complication rates and risk factors within a population based screening program. JBW Rietbergen, AE Boeken Kruger, R Kranse, FH Schröder. UROLOGY 1997; Vol 49: 875-880.*

Introduction

In 1937 Astraldi described a technique for biopsy of the prostate gland through a rectal approach [1]. Since then the technique has been greatly modified. At present, prostate biopsies are performed as an out-patient procedure without need even for local anesthesia. The main improvements in technique are the use of thin needles and of fast, automatic biopsy devices. These technical improvements have greatly reduced the discomfort of the patients as well as the costs of the procedure. Consequently the performance of transrectal ultrasonography guided systematic sextant biopsies has become the method of choice for most urologists in Europe and the US.

In recent years screening for prostate cancer has become a very important issue because the possibility of early diagnosis has been greatly improved by the use of PSA measurements. The question whether diagnosis and treatment of prostate cancer in an early stage could reduce the mortality from this disease is a major scientific issue. Screening for disease is defined as the use of diagnostic testing in the asymptomatic general population. These men generally have no complaints and are screened on a voluntary basis. Hence it is of the utmost importance that the screening procedure and the biopsy procedure is safe and the discomfort is minimal. The part of the screening procedure with the highest risk of complications is the biopsy procedure. The patients acceptance of the ultrasound guided transrectal biopsy procedure is very high, 70 to 92% of patients report no significant pain or discomfort during the biopsy procedure [2][3]. However, adverse effects and even severe complications have been described. Haemorrhagic complications are frequently seen and vary from expected minor complications as transient haematuria, haematospermia and rectal bleeding, to gross bloodloss by either route, or development of haematomas, that may require multiple transfusions [4-6]. Damage to adjacent anatomical structures has been the subject of several case reports: Ureteral trauma [7], perforation of the terminal ileum [8] and osteitis pubis [9]. A major drawback of the transrectal approach, however, is the risk of infection leading to febrile reaction, prostatitis, epididymitis, septicemia and even death [10][11].

To evaluate the safety of the screening procedure within the European Randomized Study of Screening for Prostate Cancer (ERSPC) we have evaluated the complication rates within the screened population. Identification of risk factors for the complications

that cause substantial morbidity might be of importance to improve the safety and acceptance of the screening procedure within population based screening programs.

Material & methods

Between June 1994 and July 1996 13,542 men, between 54 and 76 years old responded positively to a letter of invitation to enter the European Randomized Study of Screening for Prostate Cancer (section Rotterdam). The only exclusion criterion was a previous diagnosis of prostate cancer. Written informed consent was obtained from all study subjects. Each participant filled out an AUA7 symptom score form and a baseline-questionnaire concerning their medical history. Those who responded were randomized to either the screening or the control arm. Of the 6599 men in the screening arm 6198 men underwent all three screening tests: Digital Rectal Examination (DRE), Transrectal Ultrasonography (TRUS) and a serum prostate specific antigen determination (a cut-off value of 4 ng./ml. was used as a biopsy indication). The prostate volume was determined for all subjects using 5 mm step section planimetry. A suspicious finding by any of the three diagnostic procedures prompted a prostate biopsy.

All biopsies were performed by resident urologists in an outpatient setting. Neither Pre-biopsy bowel preparations nor cleansing enemas were used. The procedure was performed without anesthesia. Aspirin or anticoagulant therapy was stopped 10 days before the biopsy after consultation of the subscribing physician. Two hours prior and four hours after the biopsy all patients received oral antimicrobial therapy: Trimethoprim-sulfamethoxazole 960 mg. TRUS was performed using a Bruel & Kjaer model 1846 mainframe and a 7 MHz biplanar endorectal transducer with the patient in the left lateral decubitus position.

Six systematic sextant biopsies were taken during longitudinal scanning, through an oblique channel in the ultrasound probe, using a Manan® pro-mag biopsy gun and an 18 gauge (1.2mm) Bard® biopsy needle. In case of a hypoechoic lesion an additional seventh biopsy was done. This technique was described in detail by Torp-Pedersen and co-workers [12].

All patients were informed of possible complications, i.e. bleeding and infection. Special care was taken to stress the importance of medical attention in the event of fever with a temperature higher than 38.5 centigrade or severe discomfort at micturition. Both oral and written information was given.
After two to three weeks all patients were seen by one of the staff-urologists, and informed about the biopsy results. At that time a questionnaire was filled in, related to complications following the biopsy.
Three possible risk factors for complications were evaluated: A positive biopsy outcome, a prior history of diabetes mellitus and a history of prostatitis. To assess the significance of differences, concerning risk factors for complication and infection, the chi-square test with Yates' correction was used where appropriate.

Results

Cancer detection:
A total of 6,592 screening procedures was performed. For 6,198 subjects this was the first screening-visit. In this group 1,447 biopsies were performed and 36 biopsies were repeated because of a suspicious biopsy outcome requiring confirmation. Three-hundred and ninety-four men that had a negative biopsy outcome the year before were screened for the second time after a one year interval. Two-hundred biopsies were performed and 4 biopsies were repeated.
A total of 1687 procedures to obtain biopsy specimens were performed and have led to the diagnosis of 302 cases of prostate cancer.
After the first round of screening 278 (18.75%) biopsy-specimens were positive for prostate cancer. In the second round 24 (11.8%) biopsies showed prostate cancer. The 40 repeated biopsies resulted in the diagnosis of 15 (37.5%) prostate cancers.
Complication rates:
The complication rates of the biopsy procedures are specified in table 1, for all men biopsied and for four age groups. The complications were divided into two groups. Minor complications, defined as expected side effects of the biopsy procedure, causing minimal or no discomfort and requiring no additional treatment. Major complications were defined as adverse effects causing significant discomfort, disability or requiring additional treatment.

	all(#)	all(%)	<60	≥60,<65	≥65,<70	≥70
Number of men	1687		337	392	509	449
Minor complications						
Haematuria >3 days	398	23.6%	23.7%	22.19%	23.6%	24.5%
Any haematospermia	765	45.4%	62.9%	51.3%	43.8%	28.5%
Any rectal bleeding	29	1.7%	1.2%	1.5%	1.8%	2.2%
Major complications						
Pain	126	7.5%	7.4%	8.4%	9.2%	4.2%
Use of analgesics	6	0.4%	/	/	/	/
Nausea/ sickness	15	0.9%	/	/	/	/
Urinary retention	7	0.4%	0.6%	0.5%	0.2%	0.5%
Allergic reaction on antibiotic prophylaxis	2	0.12%	/	/	/	/
Perineal swelling	2	0.12%	/	/	/	/
Fever >38.5 °C	71	4.2%	3.6%	3.6%	4.9%	4.2%
Antibiotic therapy	52	3.1%	2.4%	2.8%	3.1%	3.8%
Hospitalization	7	0.4%	/	/	/	/
Sepsis	3	0.18%	/	/	/	/

Table 1:
Complication rates of 1687 transrectal prostate biopsies in total numbers and percentages for all men biopsied. Complication rates in percentages for four age groups:
1:<60; 2:≥60,<65; 3:≥65,<70; 4:≥70.

Minor complications:

Most men reported bleeding in sperm (23.6%) or urine (45.4%). Only 1.7% of men reported rectal bleeding. The haemorrhagic complications were never reason for hospitalization.

Major complications:

Pain after biopsy was reported by 126 men (7.5%) but only 6 men (0.36%) used analgesics after the biopsy. Almost one percent of subjects experienced nausea or sickness immediately after the biopsy procedure. Three men reported to have felt ill during one or more days following biopsy but they did not contact a physician. Seven men (0.4%) complained of urinary retention. They received an indwelling catheter which was removed within a week. Five of these men had an AUA7 symptom score below 10 (range 3 to 35). The planimetric prostate volume ranged from 30cm^3 to 148cm^3, two men had prostates larger than 50cm^3. Two patients noticed a perineal swelling that disappeared spontaneously and did not need any medical attention.

Seventy-one subjects (4.2%) developed fever within 10 days after biopsy, 52 (3.1%) needed antibiotic therapy and six were admitted for parenteral antibiotic therapy. Three patients showed signs of sepsis and had positive cultures of both blood and urine, one of them was admitted on the intensive care unit for two days with sepsis and shock. Three other admitted patients had high fever and clinical signs of cystoprostatitis. One of these patients had a positive urine culture but the blood culture was sterile, in the other patients both urine and blood cultures remained sterile. All positive cultures showed a Trimethoprim-sulfamethoxazole resistant Escherichia Coli. All patients recovered within a week.

The seventh admission was because of arrhythmia, this patient was discharged after two days, no explanation was found for his symptoms.

Age related complication rates:

In table 1 the complication rates are specified for four age groups: ❶ Men younger than 60, ❷ men between 60 and 65, ❸ men between 65 and 70 and ❹ those older than 70 years. The rate of haematospermia decreased with an increasing age ($P<0.001$). The rates of retention, pain and fever did not show significant differences over the age groups. Rectal bleeding showed a slightly increasing trend with increasing age but this was not significant ($P=0.72$).

Risk factors:

The relevance of possible risk factors was analyzed in all 1687 biopsied subjects. The presence of cancer in the biopsy specimen was not associated with fever, pain or hospital admission after biopsy. Statistical independence of occurrence of complications, haematuria, haematospermia, pain after biopsy and infection after biopsy in combination with the biopsy outcome was tested by means of the Chi-square test with Yates' correction. Table 2 shows the number of men with a riskfactor and the number and percentages for complications within the groups. Both occurrence of haematuria and haematospermia and the biopsy outcome were found to be dependent events. This dependence is significant with a P value of resp. 0.006 for haematuria and 0.0004 for haematospermia. Haematuria was present in 17.5% of men with prostate cancer and in 24.9% of men without cancer. Haematospermia was present in 36.1% of men with prostate cancer and in 47.4% of men without cancer.

The subjects with a former history of prostatitis and diabetes showed a slightly higher infection rate of 4.6% and 7%, but this was not significant with P values of resp. 0.87 and 0.22.

Risk factor	*N*	*Complication*	*P value*	*Fever*	*P value*
prostatitis	65	42 (64.6%)	p= 1.0	3 (4.6%)	p=0.87
Diabetes	71	48 (67.6%)	p= 0.59	5 (7%)	p=0.22
prostate cancer	302	182 (60.3%)	p= 0.08	11 (3.6%)	p=0.59

Table 2:
Possible risk factors for complications after biopsy.
Abbreviations:
N: *Number of biopsies done in patients with the risk factor.*
Complication: *Number and percentage of patients with the risk factor and any complication.*
Fever: *Number and percentage of patients with the risk factor and fever > 38.5°C after biopsy.*

Discussion

Screening for prostate cancer may reduce the mortality caused by this disease. Adverse effects and complications from the diagnostic procedures should be of minimal consequence for the quality of life within the screened population of "healthy men". TRUS guided systematic sextant biopsy is the standard method for the diagnosis of prostate cancer for most urologists in Europe and the US. The examination is easy to perform and causes little discomfort to the patient[2][3].
Complications, however, do occur and biopsy related mortality has been described [10][13][14]. The most severe complications are those caused by infection. Some authors advocate transperineal biopsy techniques because of the increased risk of bacteremia after transrectal prostatic needle biopsy [15]. The transperineal biopsy technique has a lower complication rate [15] but there have been several reports of needle tract seeding of prostate cancer. Incidence rates up to 1% have been described [16]. To our knowledge there has only been one case report of clinically evident needle tract seeding after transrectal biopsy of the prostate [17]. Bastacky and coworkers reviewed 350 previously biopsied clinical stage B radical prostatectomy specimens and identified a 2% incidence (7 cases) of needle biopsy associated tumor tracking. Five of these seven biopsies were performed transrectally. The extension into soft tissue, which was

microscopic in all cases, ranged from 0.1 to 1.2 cm. No positive margins due to tumor tracking were found [18]. In our series there has been no clinical evidence of needle tract seeding after transrectal biopsy.

The evaluation of the complication rates within the ERSPC population showed that 64.6% of all biopsied men experienced adverse effects of the biopsy procedure. Minor complications as haematospermia and haematuria for more than 3 days appeared to be the most frequent complications but medical attention was never necessary.

Haemorrhagic complications have been reported frequently (table 3) with haematuria rates varying from 1.6% [10] (where only gross haematuria was reported) to as high as 58.4% where any haematuria was reported. In the latter study 20 % still had macroscopic haematuria 3 days after biopsy [19]. Haematospermia rates varied from 5.7% to 46% [20][21]. Blood in the stool was reported less frequently (1.7%). The rates within our series compare favorably to the rates in other reports.

One-hundred and twenty-six men (7.5%) complained of pain following biopsy. Only six of them reported the use of analgesics. Unfortunately the questionnaire used was not designed for further specification of this issue. In two other reports similar rates were described (table 3)[3][20].

		reference	*N*	*HU%*	*HS%*	*RB%*	*pain%*
Torp-Pedersen	1989	[12]	138	37	5	9.4	/
Gustafsson	1990	[20]	145	39.3	46	/	6.2
Aus	1993	[3]	391	13	9	2.8	6.9
Clements	1993	[2]	80	20	11.25	7.5	/
Collins	1993	[19]	89	58.4	28.1	37.1	/
Hammerer	1994	[21]	612	14.4	5.7	2.3	/

Table 3:
Literature review of haemorrhagic complications in percentages.
Abbreviations:
N: Number of patients; HU: Haematuria; HS: Haematospermia;
RB: Rectal bleeding; Pain:Pain after biopsy

This subject deserves to be further investigated to determine whether the rate of this complication can be diminished. Urinary retention after biopsy only occurred in 7 patients. These patients had no previous diagnosis of urinary retention. Their AUA7 symptom score and prostate volume could not have predicted this complication.

The risk of infection is a frequently discussed problem. Sepsis is undoubtedly the most hazardous complication. In our series only 1 case of life threatening sepsis has occurred. The patient was admitted on the intensive care unit for two days but recovered

completely. Fever was reported by 4.2% of the biopsied men in spite of antibiotic prophylaxis. Of these men 3.1% needed medical attention and were treated with antibiotics. Six men (0.4%) were admitted to a hospital.

Infection rates varying from 2.6% up to 27.4% have been reported, however, most patients did not receive antibiotic prophylaxis[22]. The men that did receive antibiotic prophylaxis showed a lower fever rate of 18.9% versus 36.2% in the untreated group [14]. Gustafsson and co-authors also report a higher infection rate in a series of men that did not receive such prophylaxis. Torp-Pedersen and co-workers report a much lower infection rate of 1.5% in a population of 138 biopsied patients. Thirty-four patients received prophylactic antibiotics. In the group of 104 men that did not receive prophylaxis the infection rate was 2%. This difference was not significant. One explanation for the higher infection rate in our series might be that six or seven biopsies were taken instead of two or three, which could increase the infection risk.

The infection rates in the ERSPC population are comparable to those specified in other reports (Table 4). Our study does not support any conclusions regarding the use of prophylactic antibiotic therapy.

Author	*year*	*reference*	*N*	*AB*	*inf.%*	*fever%*	*hosp.%*	*sepsis%*	*death%*
Ostroff	1962	[24]	74	Y	5.4	5.4	9.5	5.4	0
Davison	1971	[14]	113	Y/N	27.4	27.4	/	3.54	1
Davison	1971	[14]	58	Y	/	18.9	/	/	/
Davison	1971	[14]	55	N	/	36.2	/	/	/
Gustafsson	1990	[20]	145	N	/	6.2	3.5	/	0
Cooner	1990	[23]	835	Y/N	/	/	0.7	0.6	0
Cooner	1990	[23]	629	Y	/	/	/	0.5	0
Cooner	1990	[23]	206	N	/	/	/	1.0	0
Aus	1993	[3]	391	Y	4.1	2.6	1.8	/	0
Clements	1993	[2]	80	Y	/	2.5	1.25	/	0
Collins	1993	[19]	89	Y	/	4.5	0	0	0
Norberg	1994	[22]	347	Y	2.6	2.6	1.2	0.3	0
Aus	1996	[21]	491	Y	7.9	3.9	0.8	/	/

Table 4:
Literature review of infectious complications in percentages.

Abbreviations:
N: Number of patients; AB: Antibiotic prophylaxis Y(es) or N(o); inf.: Symptoms of infection. fever: Fever following biopsy; Hosp.: Hospitalization; sepsis: Sepsis following biopsy. death: Death due to biopsy; /: not reported.

It is possible that sustained use of antibiotics or the use of antibiotics with broader coverage will reduce the infection rate. However, this may cause other adverse effects and promote the development of resistant bacterial strains.

The hospitalization rates in the reviewed literature vary from 0.7% to 9.5% [23][24]. In comparison to the reviewed reports the hospitalization rate is very low with 0.4% even if we include the two patients that were admitted three weeks after the cut-off date of this evaluation this rate will not exceed 0.5%.

Much is to be gained through identification of high risk patient groups for post biopsy infection. Aus and co-workers demonstrated that risk factors such as a former history of diabetes or prostatitis have a clear impact on the risk of developing an infection after transrectal biopsy of the prostate [25]. We have not been able to reproduce those results. The infection rates for men with a history of prostatitis were almost identical to those in men without such history. In the subset of men with diabetes 7% developed fever in contrast to the 4.1% of men without diabetes that developed fever. This difference, however, was not significant within our population.

The assessment of cancer as a risk factor for complications demonstrated that haematospermia and haematuria are less frequently seen in men with prostate cancer in the biopsy specimen. The explanation for this phenomenon remains uncertain. It might imply that the threshold for reporting these complications is higher after having received bad news. Evaluation of the age related complication rates (table 1) does not identify age as a risk factor for post-biopsy complications. Haematospermia decreases with an increasing age. This was observed in both men with and without the diagnosis of prostate cancer and might be explained through the fact that the sexual activity decreases with increasing age.

Conclusions

While the overall complication rate seems to be high, there were very few serious events, most complications were mild and experienced as acceptable by the participants. This is also reflected in a low refusal rate at repeat-biopsy after one year (8.8%) and favorable attendance and acceptability figures. Process evaluation data show that ninety five percent of participants would participate again [26]. The complication rates of the TRUS guided core biopsy procedure within a population based screening program are fully comparable to those reported within referred patients. Risk factors for infection after biopsy could not be identified within this biopsied series. However, minimizing the risk of infection remains an important issue.

Careful counseling before the biopsy procedure remains very important in order to minimize the patients anxiety and to assure that if complications occur they are dealt with adequately. Transrectal ultrasound guided systematic sextant biopsy of the prostate is a safe procedure for the diagnosis of prostate cancer in the general population.

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Chapter VI

Repeat screening for prostate cancer after 1-year followup in 984 biopsied men: Clinical and pathological features of detected cancer *.

John B.W. Rietbergen, Arto E. Boeken Kruger, Robert F. Hoedemaeker, Chris H. Bangma, Wim J. Kirkels and Fritz H. Schröder.

Abstract

The objective of this study is to describe the yield of a repeat examination and biopsy procedure one-year after an initial negative biopsy. We also assessed the parameters responsible for the failure to diagnose these cancers at the primary screening.
Methods: A total of 8,103 men, randomized to the screening arm of the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer were screened using PSA, DRE and TRUS. At the primary screening 1,875 men were biopsied . Prostate cancer was diagnosed in 374 men. Of the remaining 1,501 men, 984 underwent repeat screening.
Results: Biopsy at repeat screening diagnosed prostate cancer in 49 of 442 men (11%), a rate significantly lower than the 19.9% true positive biopsy rate at the primary screening. Pathological characteristics of the tumors diagnosed were not significantly different in the two groups. However, prostate volume in men diagnosed with prostate cancer was significantly greater at repeat versus primary screening (mean 42.6 cc versus 34.9 cc, $p = 0.003$). The clinical characteristics were more favorable because of an increased proportion of stage T1C tumors. Prostate volume in men with stage T1C cancer was significantly greater than in those with palpable or visible tumors in whom PSA values were in the same range.
Conclusion: The most important factor responsible for failure to diagnose these cancers at the primary screening was the significantly higher prostate volume. The tumor characteristics were not significantly different in the groups. If prostate cancer screening

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* *Repeat screening for prostate cancer after 1-year followup of 984 biopsied men: Clinical and pathological features of detected cancer. JBW Rietbergen, AE Boeken Kruger, RF Hoedemaeker, ChH Bangma, WJ Kirkels, FH Schröder. Journal of Urology 1998; vol 160: in press.*

ever becomes a routine or health care policy, efforts will have to be made to improve the chances of diagnosing prostate cancer in larger prostates by repeat biopsy procedures or by increasing the number of cores obtained.

Introduction

Although it is controversial due to a lack of evidence in randomized screening studies, secondary prevention of prostate cancer through early detection and treatment is widespread. For detecting prostate cancer in asymptomatic cases serum prostate specific antigen (PSA) determination, digital rectal examination and transrectal ultrasound have led to an increasing number of prostate biopsies and clinically diagnosed cases of prostate cancer. However, biopsy results are negative in the majority of men who undergo biopsy because of abnormal test results. It is well recognized that cases of prostate cancer are missed at biopsy [1, 2].

The introduction of six random systematic core biopsies by Hodge et al. [3] increased the accuracy in diagnosing prostate cancer. Recently Eskew et al. described the method of systematic 5 region prostate biopsy, which may further increase the diagnostic yield [4]. Others have recommended repeat biopsies for such specific indications as persistently elevated serum PSA [5] and abnormal histological findings in the initial biopsy specimen [6, 7, 8], to reduce the proportion of prostate cancer missed by initial biopsy.

In this context it is of interest to know what the yield of a selective repeat examination procedure is and whether there are any parameters that might explain why cancers diagnosed at repeat screening were not diagnosed by the primary biopsy. In this chapter we describe prostate cancer detection in relation to such clinical features as PSA, prostate volume and the clinical and pathological characteristics of cancers detected after repeat examination in 984 men in whom biopsy results were negative in the initial round of a population based screening study. Evidently our study comprises a highly select group of men and the results are not applicable to the issue of repeat screening in a population based setting.

Methods

Population:

Between October 1991 and July 1996, 17,006 men between 55 and 76 years old responded to a letter of invitation to be entered in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). This large general population based study aims at randomizing 190,000 men, including 40,000 in Rotterdam, The Netherlands. The only exclusion criterion in the study was a previous diagnosis of prostate cancer. Written informed consent was obtained from all study participants. Those who responded were randomized in either the screening arm (8,593) or the control arm (8,413). Men enrolled to the control arm were not offered testing in any way.

Techniques:

Of the 8,593 men in the screening arm, 8,013 underwent determination of serum PSA concentration (Hybritech Tandem-E PSA immunoenzymetric assay (Hybritech, Inc., San Diego, CA)), Digital Rectal Examination (DRE) and Trans Rectal Ultrasonography (TRUS). The cut-off level of the PSA test was set at 4.0 ng./ml., any value greater than 3.9 ng./ml. was considered elevated. At digital rectal examination and transrectal ultrasound the screening team was blinded to the PSA results. Nodularity, induration and asymmetry of the prostate were considered abnormal DRE results. Biplanar transrectal ultrasonography was performed, using a Bruel & Kjaer® model 1846 mainframe and a 7 MHz endorectal transducer (B&K Medical Systems, Marlborough, MA). The sonographic criteria for prostate cancer described by Lee et al. were used [9]. The prostate volume was obtained through a planimetric measurement using a 0.5 cm step-section technique.

Beginning in October 1995, DRE and TRUS were not performed in men with PSA levels below 1 ng./ml. [10].

TRUS guided systematic sextant biopsies were performed by a resident urologist, using a pro-mag® 2.2 biopsy gun and an 18 gauge Bard® biopsy needle. In case of a hypoechoic lesion, the lesion was sampled in addition. In case of high-grade prostatic intraepithelial neoplasia (PIN) or atypia the biopsy was repeated within 3 months. Men in whom the results of the primary or repeat biopsy were negative were invited to undergo a repeat examination after 1 year, according to the screening algorithm. The screening team was blinded to the results of the primary screening.

Pathology:

Tumor volume of the radical prostatectomy specimens processed at our hospital was determined using a KS400 Kontron digital morphometric analysis imaging system (Kontron electronic GmbH., Eching, Germany). Tumor grading was done according to the M. D. Anderson grading system because pathological evaluation of the radical prostatectomy specimen was performed at the hospital in which the patient was treated, and not all of those institutions use the Gleason score.

Clinical Stage of diagnosed cancers:

The 1992 TNM classification was used for the description of the clinical stage [11]. Tumor stage was determined at the time of screening, while lymph node and metastatic stages were determined at the hospital in which each patient was treated.

Statistical methods:

The chi square test was used to assess the significance of differences in the primary screening and repeat screening results in regard to cancer detection rate, clustered PSA differences in men with positive and negative biopsy results, and stage and grade distributions.

The Mann-Whitney U test was used to assess differences in prostate volume and PSA values in the primary and repeat screening groups.

Results

Primary screening

Population:

A total of 8,013 men were screened in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The serum PSA level was less than 4 ng./ml. in 6,949 men (86.7%) of whom biopsy was indicated by abnormal digital rectal examination and/or transrectal ultrasound findings in 1,139 (16.4%). In 1,064 patients (13.3%) serum PSA was 4 ng./ml. or greater, which was the indication for performing biopsy. Overall biopsy was indicated in 2,203 men, including 328 who did not undergo the procedure for various reasons.

Cancer detection:

Systematic sextant biopsies were performed in 1,875 men, which has led to the diagnosis of 374 cases of prostate cancer at an overall detection rate of 4.7% and a the true positive

biopsy rate of 19.9%. At PSA levels less than 4 ng./ml. 943 systematic sextant biopsies were performed and 100 cases of prostate cancer were diagnosed (10.6% true positive biopsy rate). At PSA levels greater than or equal to 4 ng./ml. 932 biopsies were performed and 274 cases of prostate cancer were diagnosed (29.3% true positive biopsy rate).

Repeat screening

Repeat screening population:

In 1,501 men the initial biopsy results were negative. These men were invited for a repeat screening visit 1 year later. To date 984 subjects have been screened, resulting in 498 biopsy indications. The remaining 486 men were not biopsied for various reasons: In 280 men, abnormalities on DRE and/or TRUS could not be reproduced. In 136 men the serum PSA level was below 1 ng./ml.. In 60 men the PSA level decreased below 4 ng./ml. and DRE and TRUS findings were normal. Ten men dropped out of the study.

Cancer detection after repeat examination of 984 biopsied men (Table 1):

In 632 men the PSA level was below 4 ng./ml.. DRE and/or TRUS were abnormal in 146 men, of whom 123 were biopsied. Twelve cases of prostate cancer were diagnosed (9.8% true positive biopsy rate).

Of the 352 men in whom PSA was 4 ng./ml. or greater 319 underwent biopsy and 37 were diagnosed with prostate cancer (11.6% true positive biopsy rate). Overall 49 cases of prostate cancer were diagnosed in 442 biopsies (11% true positive biopsy rate).

PSA (ng./ml.)	*Primary screening <4 ng./ml.*	*Re-screening <4 ng./ml.*	*Primary screening ≥4 ng./ml.*	*Re-screening ≥4 ng./ml.*
Screened	6,949	632	1,064	352
Biopsy	943 (13.6%)	123 (19.5%)	932 (87.6%)	319 (90.6%)
Prostate cancer	100 (1.43%)	12 (1.9%)	274 (25.8%)	37 (10.5%)
True positive biopsy rate	10.6%	9.8%	29.4%	11.6%

Table 1:

Numbers of men screened, biopsied, diagnosed with prostate cancer and true positive biopsy indications in the primary round of screening and in the repeat screening after 1 year, for PSA <4 ng./ml. and PSA ≥4 ng./ml..

Comparison of the primary screen visit and repeat screening visits

Cancer detection

The true positive biopsy rate (percentage of cancer cases detected per number of biopsies done) is not significantly different in men in whom PSA was less than 4 ng./ml. and who underwent biopsy at primary versus repeat screening (10.6 versus 9.8%; p = 0.8 chi-square test, table 1). In men with a PSA level greater than or equal to 4 ng./ml. there is a significant difference (29.4% vs. 11.6%; p<0.0001, chi square).

Prostate specific antigen

The mean PSA value of the cancers detected in the primary screening was 11.6 ng./ml. (median 5.7 ng./ml., range 0.3 ng./ml.-315.7 ng./ml.). In the cancers diagnosed in the repeat screening the mean PSA value determined in the repeat screening was 6.4 ng./ml. (median 5.4, range 1.0 ng./ml.- 24.8 ng./ml.). This difference was not statistically significant (p=0.38, Mann-Whitney U).

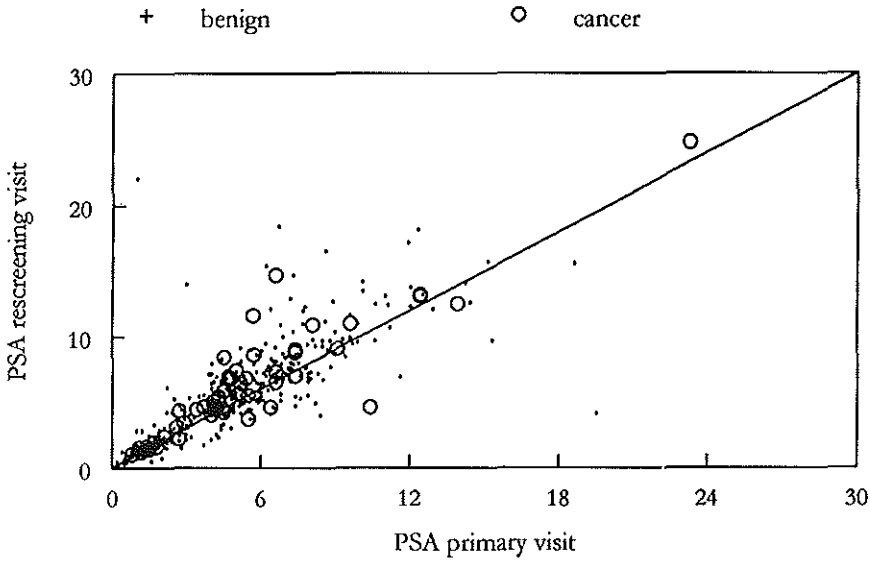

Figure 1:

PSA in the primary screening versus PSA in the repeat screening for 442 men biopsied, specified for benign biopsy outcome and prostate cancer. The line in the plot is the line of equality of PSA measured in the first and PSA measured in the repeat screening visit.

In those biopsied (N=442) the PSA value in the repeat screening visit increased in 278 men (62.9%). The mean increase in PSA was 0.6 ng./ml.. In men with prostate cancer (N=49), 35 (71.4%) had an increased PSA value in the repeat screening visit. The mean increase of the PSA level was 0.8 ng./ml.. In the 393 biopsied men with a negative outcome the PSA level in the repeat screening visit was higher in 243 (61.8%) cases with a mean increase of 0.6 ng./ml.. This difference was not statistically significant (p=0.083, Mann Whitney U). An increase of 0.75 ng./ml. or more was seen in 134 of 391 (34.3%) of men with a benign biopsy outcome and 22 of 49 (44.9%) of men with prostate cancer. This difference was not statistically significant (p=0.14, chi-square). In figure 1 the PSA value of the primary and repeat screening visit are plotted for men biopsied in the repeat screening visit.

Prostate volume:

The mean planimetric prostate volume in the primary screening group was 43.6 cc (median 37.5, range 6.4 to 224.6), while in the repeat screening group it was 53.4 cc (median 48.2, range 10.0 to 175.5). This difference was statistically significant (p <0.0001 Mann-Whitney U). Men diagnosed with prostate cancer in the primary screening showed a mean volume of 40.2 cc (median 34.9 cc, range 6.4 cc-108.5 cc). In men diagnosed with prostate cancer in the repeat screening visit the mean prostate volume (determined in the primary screening visit) was 48.3 cc (median 42.6 cc, range 21.1 cc- 116.4 cc). This difference was statistically significant as well (p=0.003, Mann-Whitney U).

In the 19 men diagnosed at repeat screening with clinical stage T1C prostate cancer mean prostate volume was 58.9 cc (median 53.2, range 28.2 to 116.7), while it was 46.2 cc (median 36.4, range 21.0 to 121.9) in men with clinical stages T2 and T3 prostate cancer in whom PSA was 4 ng./ml. or greater. This difference was statistically significant (p = 0.018 Mann-Whitney U).

Clinical stage and grade distribution (Table 2):

The clinical stage and grade distribution of the 374 cancers diagnosed in the primary screening and the 49 cases of prostate cancer diagnosed in the repeat screening is shown in table 2. In the primary screening 77 cancers (20.6%) were not organ confined. Seven of these patients had bone metastases (N=4) or lymphnode metastases (N=3). Of the 49 cases of prostate cancer diagnosed in the repeat screening two (4%) were not confined to the prostate (stage T3). No metastases were found. The difference in clinical stage distribution for organ confined versus advanced disease is statistically significant (p=0.005, chi square). Prostate cancer diagnosed at the primary screening was well

differentiated in 54% of the cases, whereas at repeat screening disease was well differentiated in 69%. This difference however, was not statistically significant (p=0.06, chi-square).

Stage / grade	Tx	T1	T2	T3	T4	T-	T-	*total*	GX	G1	G2	G3	*total*
Metastases	M0	M0	M0	M0	M0	**M+**	**N+**						
Primary round N	2	94	201	68	2	4	3	374	2	203	131	38	1122
Primary round %	0.5%	25.1%	53.7%	18.2%	0.5%	1.1%	0.8%	100%	0.5%	54.3%	35%	10.2%	100%
Repeat screening N	0	19	28	2	0	0	0	49	0	34	14	1	147
Repeat screening %	0%	38.8%	57.1%	4.1%	0%	0%	0%	100%	0%	69%	29%	2%	100%

Table 2:

Clinical stage and grade distribution of 374 cases of prostate cancer diagnosed in the primary round and 49 in the repeat screening in the Rotterdam section of the ERSPC.

Patients treated by radical prostatectomy (Table 3):

In the primary and repeat screening groups 149 (40%) and 20 (41%) men were treated with radical prostatectomy, respectively. Table 3 shows the pathological stage and grade distribution of the radical prostatectomy specimens of men diagnosed in the primary and repeat screening. Men treated by radical prostatectomy show a similar stage distribution in both groups with approximately 40% locally advanced cancers (p=0.64, chi-square). In the primary screening group 47% of cancers were well differentiated, in the repeat screening group 55% were well differentiated. This difference however, was not statistically significant (p=0.5, chi square).

	Tx	*T2*	*T3*	*T4*	*tot*	*Gx*	*G1*	*G2*	*G3*	*Tot*
Primary screening N	1	88	45	15	149	1	70	61	17	149
Primary screening %	1%	59%	30%	10%	100%	1%	47%	41%	11%	100%
Repeat screening N	0	11	7	2	20	0	11	8	1	20
Repeat screening %	0%	55%	35%	10%	100%	0%	55%	40%	5%	100%

Table 3

Pathological stage and grade distribution of 149 radical prostatectomies from the primary screening and 20 radical prostatectomies from the repeat screening group in numbers and percentages.

The prostate volumes of men treated by radical prostatectomy differed significantly among men from the primary and repeat screening group (p=0.038, Mann-Whitney U). The mean prostate volume in the primary screening was 37.2 cc (median 32.8 cc, range 15.4 cc-99.7 cc). In the repeat screening the mean prostate volume was 46.6 cc (median 41.5 cc, range 22.7 cc-116.4 cc). The PSA values however, were not significantly different (p=0.4, Mann-Whitney U). The mean PSA value in the primary screening was 6.5 ng./ml. (median 5.6 ng./ml., range 0.4 ng./ml.-31.8 ng./ml.). In the repeat screening the mean PSA value was 6.2 ng./ml. (median 6.2 ng./ml., range 1.0 ng./ml.-13.2 ng./ml.).
The tumor volume is known in 71 men with prostate cancer diagnosed at a PSA level greater than or equal to 4 ng./ml. and treated by radical prostatectomy in our institution. Sixty of these men were diagnosed in the primary screening round and 11 in the repeat screening. The tumor volumes did not differ significantly (p=0.14, Mann-Whitney U). The mean tumorvolume of men diagnosed in the primary screening was 1.6 cc (median 1.0 cc, range 0.1 cc-13.5 cc), the mean tumorvolume of men diagnosed in the repeat screening was 0.8 cc (median 0.7 cc, range 0.04 cc-1.9 cc). There was no significant difference in PSA value between the two groups (p=0.87, Mann-Whitney U).

Discussion

The frequency of screening and subsequent performance of biopsy procedures is a trade-off between unnecessary testing and the risk of missing potentially curable cancer that may pose a threat to the wellbeing of the host within his life span. Recently Stroumbakis et al. showed that in 20% of 89 men with biopsy proven prostate cancer the second biopsy was negative [1]. In a study by Keetch and associates [5], repeat biopsies were done because of a persistent elevated PSA level in combination with abnormal findings by DRE and/or TRUS in men initially biopsied for the same reasons. They showed a 19% true positive biopsy rate. In our series, men with PSA levels ≥4 ng./ml. were biopsied, regardless of the DRE and TRUS findings, which resulted in a true positive biopsy rate of 11.6%. Men biopsied above the PSA threshold with abnormal findings by DRE and/or TRUS showed a true positive biopsy rate of 15.7%, which is comparable to the series of Keetch et al..

We found no significant difference in true positive biopsy rates at PSA levels below 4 ng./ml. in the primary and re-screening group (Table 1). A considerable number of men was not biopsied in the repeat screening since the abnormal DRE and TRUS findings in the primary screening could not be reproduced. The mechanisms that may have had a role were high interexaminer variability during digital rectal examination [12] which was most important, and the fact that reversible conditions, such as prostatitis, may cause abnormal digital rectal examination and transrectal ultrasound findings. However, the selection of men in whom digital rectal examination and transrectal ultrasound findings are abnormal seems to maintain the true positive biopsy rate at repeat screening at almost the same level as at primary screening.

The PSA distribution did not differ significantly among patients diagnosed in the primary and repeat screening visit ($p=0.38$, Mann-Whitney U). The initially measured prostate volume of men with prostate cancer was significantly higher in men from the repeat screening group (a mean volume of 48.3 cc versus 40.2 cc ($p=0.003$, Mann-Whitney U)). It has been shown that prostate size as well as tumor characteristics may influence cancer detection [13, 14]. In the subset of men treated by radical prostatectomy, the pathological characteristics of tumors diagnosed in the primary and repeat screening were identical. Both groups showed capsular penetration in approximately 40% of patients. The tumor volumes did not differ significantly ($p=0.14$, Mann-Whitney U), however, there was a trend towards lower tumor volumes in the repeat screened group which may not have

been.significant due to the low number of men in the repeat screening group. The PSA distributions did not differ significantly in spite of the fact that the median PSA value in the repeat screening was slightly higher. The prostate volume however, was significantly higher in the repeat screening group (p= 0.003, Mann-Whitney U) which must have reduced the chance of diagnosis in the primary screening visit. This confirms findings by Eskew et al. [4] who showed that a volume based biopsy pattern will enhance the yield of the biopsy procedure in terms of cancers diagnosed.

Despite the identical distribution of pathological stage in the two groups the distribution of clinical stage in the men with prostate cancer diagnosed at repeat screening was significantly more favorable than in the primary screening group. The percentage of T1C cancers nearly doubled and only four percent of men had clinical signs of extracapsular growth. Both Epstein and coworkers and Oesterling and coworkers [15, 16] independently showed that T1C cancers were diagnosed in prostates with significantly higher volumes which may explain why these tumors are impalpable. Our findings in the repeat screened group were in line with these observations. Prostates harboring T1C cancers were significantly larger (median 53.2 cc) than those harboring T2 or T3 cancers at a PSA level≥4 ng./ml. (median 36.4 cc). Half of the 20 men treated by radical prostatectomy had stage T1C cancer. Four of these were pathologically organ confined. Nine men had stage T2 disease of whom 7 had organ confined disease. One patient had clinical stage T3A disease which was also the case in the radical prostatectomy specimen. The fact that higher prostate volumes lead to underestimation of extracapsular disease in T1C cancers and that the percentage of stage T1C cancers nearly doubled due to the higher prostate volumes in the repeat screening resulted in a more favorable clinical stage distribution when compared to the pathological stage distribution.

An additional explanation for the diagnosis of prostate cancer in men with a negative biopsy outcome in the primary screening could be the presence of small but rapidly growing tumors which would enhance the detection chance at repeat screening. Carter et al. [17] reported that on serial measurements the rate of increase in serum PSA was higher in patients with prostate cancer than in those with benign conditions of the prostate. A PSA velocity cutoff point of 0.75 ng./ml. was suggested. In our series of 442 re-biopsied men the mean increase of PSA in men with prostate cancer was 0.8 ng./ml. versus 0.6 ng./ml. in men with negative biopsy results. This trend however, was not statistically significant (p=0.083, Mann-Whitney U). An increase of 0.75 ng./ml. or more was seen in 34.3% of men with a negative biopsy result and in 44.9% of men with

prostate cancer. This difference was not significant either (p=0.14, chi-square). In figure 1 this overlap is shown in a scatterplot. Pearson and Carter [18] demonstrated that cancer cases showed an early linear phase of PSA increase followed by an exponential phase. Since the increase of PSA in men with and without prostate cancer did not differ significantly it can safely be assumed that diagnosis in the repeat screening visit is not caused by tumors with a short PSA doubling time. As suggested by Carter, a longer observation period of two years may be necessary to study on the value of "PSA velocity" in this situation.

Conclusion

The significantly higher prostate volume seems to have a key role in the diagnosis of prostate cancer in the repeat screening visit as well as in the increase of the proportion of T1C disease. Our results indicate that the chance of diagnosing prostate cancer in men with a large prostate is reduced. Patients treated by radical prostatectomy from both the primary and repeat screening group show a similar pathological stage distribution. The tumorvolumes did not differ significantly; however, it can not be excluded at this time that the trend towards smaller tumors in the repeat screening group will become significant with increasing numbers. If early detection and treatment are able to decrease prostate cancer specific mortality the diagnosis of cancers in larger prostates should be improved by either repeat biopsies or increasing the number of cores in the initial biopsy in men with high prostate volumes since the characteristics in terms of proportion of extracapsular tumors are often unfavorable.

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Part C

Cancers Detected

Chapter VII

The changing pattern of prostate cancer at the time of diagnosis: Characteristics of screen detected prostate cancer in a population based screening study. (ERSPC data Rotterdam) *.

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Abstract

The clinical and pathological features of prostate cancer diagnosed through serum PSA, Digital Rectal Examination (DRE) and Trans Rectal Ultra-Sonography (TRUS) in a population based randomized screening study are described.

Methods: Between November 1993 and June 1997, 20,632 volunteers aged between 55 and 76 years were included in the study. In the screening arm 9,776 men underwent DRE, TRUS and a serum PSA determination. Biopsies were taken if the findings at DRE and/or TRUS were abnormal or if the PSA level was greater than or equal to 4 ng./ml.. A total of 2,262 men underwent a biopsy procedure and 474 cases of prostate cancer were diagnosed.

Results: The pre-treatment data were complete in 459 men. Clinically organ-confined disease was seen in 78% of men. Bone or lymphnode metastases were seen in 8 cases (1.7 %). In two of the 172 men who underwent a radical prostatectomy, lymphnode metastases were seen. Organ confined disease was seen in 66.3% of men treated by radical prostatectomy.

Conclusion: Comparison of the characteristics of prostate cancer detected through screening of the general population with the features of a series of incident cases in a population based cohort of men where no organized screening for the disease took place shows a dramatic stage reduction, mainly expressed in the proportion of metastasized cases. Whether this stage reduction will lead to a decrease in disease specific mortality remains unknown until the study has been finished, and the endpoint, prostate cancer specific mortality can be evaluated.

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* *The changing pattern of prostate cancer at the time of diagnosis: Characteristics of screen detected prostate cancer in a population based screening study. (ERSPC data Rotterdam). JBW Rietbergen, RF Hoedemaeker, AE Boeken Kruger, WJ Kirkels, FH Schröder. Submitted 1998.*

Introduction

Prostate cancer is a serious health problem in elderly men. In the Netherlands it is the second leading cause of male cancer deaths. The most recent report of the Netherlands Cancer Registry [1] shows a cumulative risk of being diagnosed with prostate cancer between the age of 0 and 74 of 6.26 %. The risk of developing prostate cancer from age 55 until death is 9.9%. The cumulative risk of prostate cancer specific mortality without age limits is estimated on 2%.

Prostate cancer develops unnoticed within the prostate; even metastatic disease may exist with no signs or symptoms for years. Many of the clinically diagnosed cancers have already spread outside the prostate before the first diagnosis is made. The prognosis of patients with advanced prostate cancer is poor. Cure is impossible and once metastases to bone occur the median survival is in the range of 180 weeks in spite of endocrine treatment [2].

At this time the most promising way to control prostate cancer and to reduce mortality seems to be through early detection and treatment. Screening of the male population in the high-risk age group however is still controversial. This controversy is based on a marked discrepancy between prevalence and mortality. Autopsy studies have shown that approximately 30 % of all men who come to necropsy harbor latent prostate cancer [3]. In series of cystoprostatectomy specimens obtained from men with normal digital rectal examinations operated for a pathological condition of the bladder a 38% to 46% incidence has been observed [4, 5]. Most of these tumors however are different from those detected clinically. Their volumes are smaller (mean 0.11 ml, range 0.01-1.10 ml). These cancers are often well differentiated and usually confined to the prostate. In contrast, only 10 to 15% of screen detected cancers have the features of autopsy cancers [6, 7]. Furthermore, 97% of these tumors were organ confined, 3% had extracapsular extension and none demonstrated positive surgical margins, seminal vesicle invasion or positive lymph nodes.

In several European countries as well as in the U.S.A. randomized screening studies are conducted with prostate cancer mortality as the major endpoint in order to find a possible solution to the present controversy [8]. In this chapter the characteristics of prostate cancers detected in the first round of screening in the ERSPC section Rotterdam are described. The relationship between the clinical and pathological

characteristics is assessed. Furthermore, a comparison is made with reports from literature describing features of prostate cancer diagnosed through screening and incident cases of prostate cancer in the general population.

Methods

Patient population:

Between November 1993 and June 1997, 20,632 men between 55 and 76 years old responded to a letter of invitation to enter the European Randomized Study of Screening for Prostate Cancer (Section Rotterdam). The response rate was 42%. The only exclusion criterion for participation in the study was a previous diagnosis of prostate cancer. Written informed consent was obtained from all study subjects. Those who responded were randomized to either the screening arm or the control arm. The 10,183 men in the control arm were not offered testing in any way.

Of the 10.449 men in the screening arm 9,776 men underwent a serum PSA determination, digital rectal examination and transrectal ultrasonography. The remaining 673 did not show up on the scheduled screening visits.

Techniques:

All men underwent a determination of serum PSA concentration (Hybritech Tandem-E PSA immunoenzymetric assay (Hybritech, Inc., San Diego, CA)), blood samples were drawn before the other tests were performed. The cut-off level of the PSA test was set at 4.0 ng./ml., any value greater than 3.9 ng./ml. was considered elevated. At the time of screening the members of the screening team were not aware of the PSA results.

Digital rectal examination was performed by a resident urologist or an ultrasound-technician; Nodularity, induration and asymmetry of the prostate were considered abnormal.

Biplanar transrectal ultrasonography was performed by a resident urologist or an ultrasound technician using a Bruel & Kjaer® model 1846 mainframe and a 7 MHz endorectal transducer (B&K Medical Systems, Marlborough, MA) with the subject in the left lateral decubitus position. The sonographic criteria for prostate cancer described by Lee et al. were used [9]. An abnormality by any of the three diagnostic tests prompted a sextant prostate biopsy. Quality control showed there was no significant difference in prostate cancer detection among the residents and the ultrasound technician. All prostate biopsies were performed under ultrasound guidance, by a resident urologist,

using a pro-mag® 2.2 biopsy gun and an 18 gauge Bard® biopsy needle. If the biopsy indication was an elevated PSA level or an abnormal digital rectal examination sextant biopsies were performed. In case of a hypoechoic lesion, the lesion was sampled in addition to the sextant biopsy. All subjects received antimicrobial prophylaxis (Co-trimoxazole 960 mg P.O.) two hours prior and four hours after the procedure. The pathological findings from the biopsies were the reference test for determining the presence or absence of prostate cancer.

All subjects were informed about the biopsy outcome in our institution. In case of a positive biopsy result the patients were informed about the various treatment options. The family physician was informed on the same day. The patients were referred to the hospital of their choice by their family physician. The choice of treatment was made after consideration of all facts by both the Urologist and the patient. Information about the pretreatment evaluation of 459 patients is available and was obtained by reviewing the patient records in the various hospitals.

Clinical Stage of diagnosed cancers:

The TNM classification of 1992 was used for the description of the clinical stage [10]. The stage as described at the time of the screening visit was used as Tumor stage. Stage T1C prostate cancer is defined as impalpable and invisible at the time of TRUS diagnosed on needle biopsy. We have added a separate category of impalpable prostate cancer, regardless of the findings on TRUS to improve the comparability of our series with series from other centers where TRUS is not used for the diagnosis of prostate cancer.

The Lymphnode and Metastases stage was determined in the hospital where the patients were treated. All men who underwent a radical prostatectomy had a pelvic lymphnode dissection. If the frozen sections were negative, the clinical stage was considered N0. Those treated with radiotherapy had a CAT scan of the prostate as well as of the regional lymph nodes for planning of the radiation field. The scans were reviewed by a Radiologist and the lymphnode status was described. Twenty patients had an additional pelvic lymphnode dissection because of a high PSA value. Men treated by watchful waiting (N=36) had a CAT scan in 12 cases and the remaining 22 had PSA levels below 10 ng./ml..

To determine whether bone metastases were present, routine bonescans were performed. Recently, most hospitals decided not to perform bone scans in absence of bone pain, a normal serum alkaline phosphatase level and a PSA level below 10 ng./ml..

In some cases a cutoff level of 20 ng./ml. was used [11, 12]. The biopsy grade was never reason for performing bone scans or CAT scans.

Pathology:

After routine fixation in a 4% buffered formalin solution, biopsy cores were separately embedded into paraffin blocks. Biopsy cores were longitudinally sectioned at three levels with a thickness of 5µm and standard haematoxylin-eosin-stained histological slides were prepared. The pathologists of the Rotterdam University Hospital pathology department performed routine histological examination. In case of doubts, there was a low threshold for consultation with the uro-pathological reference pathologist of the department. All biopsy specimens were graded according to both the MD Anderson and the Gleason grading system.

Immediately after radical prostatectomy the specimens were totally (including seminal vesicles) submitted to the pathology department. After fixation the radical prostatectomy specimens were inked and sectioned at 4 mm. intervals. Of each slice an H&E stained histological slide was prepared. All specimens were graded according to the MD Anderson grading system since the pathological evaluation of the radical prostatectomy specimen took place in the hospital where the patient was treated and not all institutes use the Gleason score. The radical prostatectomy specimens processed in our own institution (N=101) were graded according to the Gleason grading system as well.

Statistical methods:

Chi-square test: To assess the significance of differences in stage (intra- or extracapsular growth) and grade distribution of different PSA groups, T1C versus not T1C cancers diagnosed at PSA levels of 4 ng.ml. or higher and palpable and impalpable prostate cancer diagnosed at PSA levels greater than or equal to 4 ng./ml.., the chi-square test with Yates' correction was used where appropriate.

Kruskal-Wallis test: To assess the significance of differences in PSA distribution between the various grades of differentiation.

Mann-Whitney U test: To assess the significance of differences in PSA distribution between patients with a maximal Gleason score of 7 (pattern 3 and 4) and patients with a Gleason score of 7 (pattern 4 and 3) or higher.

Binominal test: To evaluate the probability that a random sample of 459 men from 4708 incident cases shows a similar percentage of metastasized cases and clinically organ confined prostate cancer as was the case in the screening population.

Wilcoxon paired rank test: To determine whether the MD Anderson score and the Gleason score show a difference in distribution in the biopsy specimen and the Radical prostatectomy specimen.

Results

Population:

The mean age of the screened men in this population was 63.4 (range 55-76, median 63.0). Of the 10,449 subjects in the screening group 9,776 men underwent all screening tests. In 2,373 (24.3%) subjects there was an indication for biopsy. In 111 cases the biopsy procedure was not performed for various reasons: 87 men refused a biopsy, 24 men could not be biopsied because of the use of anticoagulant therapy.

Cancer detection:

A total of 2,262 biopsies were performed. Four hundred and seventy-four prostate cancers were diagnosed resulting in an overall prostate cancer detection rate of 4.8 %. The performance of the various screening tests expressed in number of biopsies and number of cancers diagnosed is detailed in Table 1. At PSA levels below 4 ng./ml., 1,086 biopsies were performed and 123 cases of prostate cancer were diagnosed. At PSA levels greater than or equal to 4 ng./ml., 1,176 biopsies were performed and 351 cases of prostate cancer were diagnosed.

Clinical stage and grade distribution:

Table 2 shows the clinical stage distribution of 459 cases of prostate cancer diagnosed in the ERSPC section Rotterdam. Seventy-eight percent of cancers are clinically confined to the prostate. Bone sans were done in 342 patients. Men treated more recently (N=112) did not have a bone scan if the PSA value was below 10 ng./ml.. In 4 men the PSA value was below 20 ng./ml. and this was reason for not performing a bone scan. In one patient a bone scan was not performed because lymphnode metastases were present. In four cases (0.9%) bone metastases were present. Lymphnode metastases were seen in 4 cases (0.9%). Three cases were diagnosed by CAT scan and one by a pelvic lymphnode dissection because of a high PSA level prior to radiotherapy. No metastases were found in the frozen sections before radical prostatectomy. However, in two men micro-metastases were seen in the paraffin sections.

	DRE	TRUS	Biopsies	Prostate cancer	Biopsies/cancer	PPV
PSA≥4 ng./ml.	-	-	711	124	5.7	17.4%
	+	-	149	48	3.1	32.2%
	-	+	137	45	3.0	32.8%
	+	+	179	134	1.3	74.8%
PSA<4 ng./ml.	+	-	444	45	9.9	10.1%
	-	+	442	40	11.1	9.0%
	+	+	200	38	5.3	19.0%
overall			2262	474	4.8	20.1%

Table 1:
Number of biopsies, cancers detected, biopsies per cancer rate and positive predictive value (PPV) for all individual screeningtests and their combinations in men with PSA levels greater than or equal to 4 ng./ml. and men with a PSA level below 4 ng./ml..
Keys: DRE: Digital rectal Examination; TRUS: Transrectal Ultrasonography; (+): Abnormal test results; (-) Normal findings

Stage	TX	T1	T2	T3	T4	T1-4	T1-4	total
Metastases	M0	M0	M0	M0	M0	M+	N+	
	ERSPC Rotterdam Screen detected prostate cancer							
Number	-	117	240	90	4	4	4	459
%	-	25%	52%	20%	1%	1%	1%	100%
	Incident cases Amsterdam cancer registry							
Number	230	744	1846	566	183	1139	-ns	4708
%	5%	16%	39%	12%	4%	24%	-ns	100%

Table 2:
Clinical stage distribution of 459 cases of prostate cancer diagnosed in the Rotterdam section of ERSPC. -ns = not specified seperately.
Clinical stage distribution of 4708 cases of prostate cancer diagnosed between 1989 and 1994 in the Amsterdam region (Visser and Horenblas, NTvG 52, 1996 [13])

The second part of table 2 shows the clinical stage distribution of 4,708 incident cases of prostate cancer diagnosed between 1989 and 1994, reported by the Amsterdam cancer registry in the Netherlands [13]. The stage distribution of these incident cancers shows 60% of locally confined prostate cancer and 24% of metastasized cases. The probability that 1.7 percent of metastasized men or 78 percent of men with clinically localized disease would have been found in a sample of 459 men from the Amsterdam population is less than 0.001 (Binominal test).

The clinical grade distribution (grade of the biopsy specimens) shows 269 (58.6%) well-differentiated cancers, 145 (31.6%) moderately differentiated and 45 (9.8%) poorly differentiated cancers.

The Gleason score distribution of the biopsy specimens shows: 16 (3.5%) *Gleason 4*, 50 (10.9%) *Gleason 5*, 218 (47.5%) *Gleason 6*, 122 (26.6%) *Gleason 7*, 43 (9.4%) *Gleason 8*, 7 (1.5%) *Gleason 9* and 3 (0.7%) *Gleason 10*.

Cancer treatment:

Information about the pretreatment evaluation of 459 patients is available. In 4 cases (1%) the treatment choice has not been made yet. Radical Prostatectomy was chosen for the treatment in 176 (38%) patients (The radical prostatectomy was performed in 172 men, in 4 cases the pathological results are pending), 236 (51%) men received radiotherapy. Watchful waiting was chosen by 36 (8%) patients. Seven (2%) patients have received endocrine treatment, five because of metastases and two insisted on hormonal treatment for localized prostate cancer, which is not a standard procedure.

Clinical versus pathological characteristics of 172 radical prostatectomy specimens:

The clinical characteristics and pathological characteristics of men diagnosed with prostate cancer that underwent a radical prostatectomy were compared. The results are presented in Table 3, and Table 4. Table 3 shows the clinical versus the pathological stage distribution. Two men with pelvic lymphnode metastases were included in the tables and are indicated with an asterix. In both cases the metastases were not seen in the frozen sections, only in the definitive paraffin sections after performance of the radical prostatectomy. The pathological stages of these two men were: T3C N1 M0 (PSA=24.8 ng./ml.) and T2B N1 M0 (PSA=5.4 ng./ml.). In both cases the cancer was well differentiated.

#	pT0	pT2A	pT2B	pT2C	pT3A	pT3B	pT3C	pT4A	pT4B	total
T1C		*11*	*0*	*24*	*9*	*1*	*1*	*4*	*0*	*50*
T2A	1	12	3*	36	13	1	4	8	1	79
T2B		2	-	5	3	2	1	1	-	14
T2C		2	-	6	2	-	-	-	-	10
T3A		-	1	7	4	-	1*	2	-	15
T3B		1	-	-	-	-	-	-	-	1
T3C		2	-	1	-	-	-	-	-	3
T4A		-	-	-	-	-	-	-	-	0
T4B		-	-	-	-	-	-	-	-	0
total	1	30	4	79	31	4	7	15	1	172

Table 3:
Clinical versus pathological stage distribution of 172 patients that underwent a radical prostatectomy.

For the comparison of clinical intra and extra capsular disease versus pathological intra and extracapsular disease the TNM system is applied: Only capsular penetration, not capsular infiltration is accounted for as "extracapsular disease". The Stage T1C cancers are included and considered clinically intra-capsular. Of 153 men thought to have organ confined disease, 51 (33.3%) had extracapsular extension. Of 19 men with clinical signs of locally advanced disease, 12 (63.2%) had tumors limited to the prostate (intra-capsular). The clinical and pathological stage were unrelated (p=0.76, chi square)
The comparison of the biopsy MD Anderson grade with the grade in the radical prostatectomy specimen shows that 120 cases (70%) have been graded correctly. Undergrading is the case in 37 men (22%) and overgrading in 13 (8%) men. The grade in the radical prostatectomy specimens is significantly underestimated in the biopsy specimen (p=0.002, Wilcoxon paired rank).
Table 4 shows the biopsy Gleason scores versus the Gleason score in 101 radical prostatectomy specimens processed in our institution. According to the Gleason score 46% of tumors were correctly graded, 39% were under-graded and 16% were over-graded. The Gleason score in the radical prostatectomy specimens is significantly underestimated in the biopsy specimen (p<0.001, Wilcoxon paired rank).

	B 4	*B 5*	*B 6*	*B 7*	*B 8*	*Total*
p 5	2	2	12	-	-	16
p 6	1	2	22	-	-	25
p 7	2	5	22	22	4	55
p 8	-	-	1	1	-	2
p 9	-	-	1	-	2	3
total	5	9	58	23	6	101

Table 4:
Biopsy Gleason score (B) versus Gleason score in 101 radical prostatectomy specimens (p).

Pathological characteristics of 172 radical prostatectomy specimens:

The stage and grade distribution of the radical prostatectomy specimens is shown in Table 5 and Table 6. This was done for all cancers, those diagnosed at PSA levels below 4 ng./ml. and those diagnosed at PSA levels greater than or equal to 4 ng./ml., T1C cancers and not T1C cancers (visible and or palpable cancers diagnosed at PSA levels ≥4 ng./ml.) and palpable and impalpable disease at PSA levels of 4 ng./ml. or higher. Overall 114 cancers (66%) were pathologically intra-capsular. At PSA levels below 4 ng./ml. this was 84% and at PSA levels ≥ 4 ng./ml. 59% of cancers were intra-capsular. This difference is statistically significant (p=0.001, chi square). Seventy percent of T1C cancers were confined to the prostate whereas 51% of not T1C cancers were confined to the prostate. This difference was statistically significant (p=0.03, chi square). Palpable disease at PSA levels of 4 ng./ml. or higher was intracapsular in 53% of cases and impalpable disease was intracapsular in 63% of cases. This difference was not statistically significant (p=0.27, chi square).

The overall MD Anderson grade distribution of the radical prostatectomy specimens showed poorly differentiated tumors in 17 (10%) cases. The grade of differentiation was moderate in 57 (33%) cases and 96 (56%) tumors were well differentiated. In two cases the grade was not documented. At PSA levels below 4 ng./ml. 39 cancers were well-differentiated (77%) and 11 were moderately differentiated (22%). In one case (2%) the grade was not documented. There were no poorly differentiated tumors. At PSA levels ≥4 ng./ml., 57 cancers (47%) were well differentiated, 46 (38%) were moderately differentiated and 17 (14%) were poorly differentiated. In one (1%) case the grade was not documented. The observed difference in these two groups was statistically

significant (p<0.001, chi square). Furthermore a positive correlation was found between the MD Anderson score and PSA levels. Well-differentiated tumors were found at significantly lower PSA levels than moderately and poorly differentiated tumors (p<0.001, Kruskal-Wallis). T1C and not T1C cancers showed a similar MD Anderson grade distribution (p=0.95, chi square). T1C cancers were well differentiated in 23 (46%) cases, moderately differentiated in 20 (40%) cases and poorly differentiated in 7 (14%) cases. Not T1C cancers at PSA levels of 4 ng./ml. or higher were well differentiated in 34 (48%) cases, moderately differentiated in 26 (37%) cases and poorly differentiated in10 (14%) cases, in one case the grade was not documented. The difference between palpable and impalpable disease at PSA levels of 4 ng./ml. or higher was not statistically significant either (p=0.95, chi square). Palpable disease was well differentiated in 23 (45%) cases, moderately differentiated in 20 (40%) cases and poorly differentiated in 7 (14%) cases, in one case the grade was not documented. Impalpable disease was well differentiated in 34 (49%) cases, moderately differentiated in 26 (37%) cases and poorly differentiated in10 (14%) cases.

N (%)	*Confined (pT2)*	*pT3A*	*pT3B*	*pT3C*	*pT4A*	*pT4B*	*total*
All	*114 (66%)*	31 (18%)	4 (2%)	7 (4%)	15 (9%)	1 (1%)	172
PSA<4	*43 (84%)*	7 (14%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	51
PSA≥4	*71 (59%)*	24 (20%)	4 (3%)	7 (6%)	15 (12%)	0 (0%)	121
T1C	*35 (70%)*	9 (18%)	1 (2%)	1 (2%)	4 (8%)	0 (0%)	50
Not T1C (PSA≥4)	*36 (51%)*	15 (21%)	3 (4%)	6 (9%)	11 (16%)	0 (0%)	71
Impalpable (PSA≥4)	*44 (63%)*	15 (21%)	1 (1%)	4 (6%)	6 (9%)	0 (0%)	70
Palpable (PSA≥4)	*27 (53%)*	9 (18%)	3 (6%)	3 (6%)	9 (18%)	0 (0%)	51

Table 5:
Pathological stage distribution of all 172 radical prostatectomies. Stage distribution of radical prostatectomy specimens performed for 51 cancers detected at PSA<4 ng./ml.; 121 cancers detected at PSA≥4 ng./ml.; 50 T1C cancers and 71 not T1C (palpable and or visible) prostate cancers at PSA levels ≥4 ng./ml.; 70 impalpable cancers detected at PSA ≥4 ng./ml. and 51 palpable cancers detected at PSA ≥4 ng./ml. in total numbers and (row percentages).

The mean Gleason score of the 101 cases of prostate cancer treated by radical prostatectomy in our institution was 6.5 ± 0,18 (range 5 to 9). The Gleason scores are further specified in Table 6. A Gleason score of 7 was seen in 55 men (55%). Of these men, 11 had had a tumor containing more than 50% Gleason growth pattern 4. A Gleason score of 8 or higher was seen in 5 men. These tumors were all palpable and visible and the PSA value was higher than 4 ng./ml.. The observed differences in Gleason score between men with PSA levels below 4 ng./ml. and those with PSA levels equal to or higher than this threshold level did not differ significantly (p=0.34, chi square). No positive correlation was found between PSA level and Gleason score (p=0.18, Kruskall-Wallis). We did find a positive correlation between PSA and men with a Gleason score of 7 or lower and less than 50% of growth pattern 4 and men with a Gleason score of 7 or higher and more than 50% of pattern 4 (p=0.02, Mann-Whitney U).

The differences in Gleason score between T1C and non-T1C disease and palpable and impalpable disease at PSA levels of 4 ng./ml. or higher were not statistically significant (respectively p=0.20 and 0.42, chi square).

Positive surgical margins were seen in 47 of 172 radical prostatectomy specimens (27%). The prevalence of positive margins in cancers diagnosed at PSA levels under 4 ng./ml. was 10 of 51 (20%), at PSA ≥4 ng./ml. this was 37 of 121 (31%). T1C cancers showed positive margins in 13 of 50 cases (26%) and not T1C cancers had positive margins in 24 of 71 cases (34%). Palpable cancers hat PSA levels of 4 ng./ml. or higher had positive margins in 20 of 70 cases (29%) and in impalpable cancers at PSA levels of 4 ng./ml. or higher the margins were positive in 17 of 51 cases (33%). The observed differences were not statistically significant (respectively p=0.14, p=0.36 and p=0.6 chi square). If the tumor did not show pathological evidence of extracapsular growth the surgical margins were positive in 16% of cases. In case of extracapsular growth 50% of surgical margins were positive. This difference was significant (p<0.001, chi square).

N (%)	*P Gleason 5*	*p Gleason 6*	*p Gleason 7 (3+4)*	*p Gleason 7 (4+3)*	*p Gleason 8*	*p Gleason 9*	*Total*	*Mean score*	*SE*
All	16 (16%)	25 (25%)	44 (44%)	11 (11%)	2 (2%)	3 (2%)	101	6.5	0.09
PSA<4	4 (12%)	11 (33%)	165 (49%)	2 (6%)	-	-	33	6.4	0.12
PSA≥4	12 (18%)	14 (21%)	28 (41%)	9 (13%)	2 (3%)	3 (4%)	68	6.6	0.12
TIC	8 (30%)	6 (22%)	10 (37%)	3 (11%)	-	-	27	6.2	0.17
Not TIC (PSA ≥ 4)	4 (10%)	8 (20%)	18 (44%)	6 (15%)	2 (5%)	3 (7%)	41	6.8	0.15
Impalpable (PSA≥4)	10 (25%)	9 (23%)	14 (35%)	5 (13%)	1 (3%)	1 (3%)	40	6.4	0.15
Palpable (PSA≥4)	2 (7%)	5 (18%)	14 (50%)	4 (14%)	1 (4%)	2 (7%)	28	6.8	0.17

Table 6:
Pathological Gleason score distribution, mean Gleason score and standard error of the mean Gleason score correlated with PSA- and T-categories of 101 men after radical prostatectomy:

Discussion

Stage reduction:

Screening for any cancer will reduce mortality if localized cancers that are detectable include biologically aggressive cancers in a curable stage. This offers a window of opportunity during which screening may impact on mortality if used appropriately. If this requirement is fulfilled, the detection of locally confined tumors should be pursued, whereas the detection of tumors with capsular penetration and even more important, distant metastases is undesirable. The characteristics at the time of diagnosis of incident cases of prostate cancer in the Amsterdam region [13], in the period 1989 to 1994 were described by the Amsterdam Comprehensive Cancer Registry. Cases diagnosed at autopsy or cystoprostatectomy were not included. It should be noted that in the Netherlands as well as in many other European countries screening for prostate cancer is not routinely applied to the general population. The official policy of the ministry of Health is that screening for prostate cancer is only allowed in a study setting, as is the case in our study, which has been approved according to Dutch law. This implies that all cancers described by the regional cancer registries are incident cases, not diagnosed

through organized screening but some opportunistic screening takes place. The stage distribution of prostate cancer diagnosed in the Amsterdam region shows 24% metastasized cases and 60% of locally confined cancers (Table 2). In our series of 459 cancers detected in the first round of screening, 77% of cancers were locally confined, only 0.9% of men showed bone metastases and an additional 0.9% had lymph node metastases. The stage distribution of the screened population was significantly different ($p<0.001$, binominal test) from the stage distribution within the Amsterdam cohort of incident cases.

This stage reduction is an important finding which justifies the continuation of the ongoing randomized screening studies however, the uncertainty continues whether screening will decrease prostate cancer mortality.

Over-detection:

Concern has been raised that screening for prostate cancer, although it increases the detection of localized cancer, may identify tumors of little biological significance. Autopsy and cystoprostatectomy studies have shown a prevalence of 30 to 46% [3, 4]. Ohori and coworkers [5] showed that only 10 to 15% of screen detected prostate cancers have characteristics similar to prostate cancer in cystoprostatectomy specimens. Epstein et al. classified 16% of cancers as insignificant and an additional 10% as minimal disease in a series of 157 stage T1C prostate cancer treated by radical prostatectomy [14]. In contrast, some very small tumors (stage A or T1A) that were well differentiated have been shown to be potentially dangerous in patients with a life expectancy of 15 years or more [15]. In a recent study by Albertsen et al. [16] with the objective to estimate long-term survival of men aged 65 to 75 years (mean 70.9) with conservatively treated newly diagnosed localized prostate cancer two important findings were demonstrated: (1) Tumor histologic features are highly predictive of survival and (2) patient comorbidities are nearly as potent a predictor of survival as grade of differentiation. Men having low grade (Gleason score 2-4) prostate cancer (mainly diagnosed incidental on trans-urethral resection for benign prostatic hyperplasia) face no apparent loss in life expectancy compared with a relevant general population. Men with higher-grade tumors experience a progressively increasing loss of life expectancy. Since the health condition of the host has a significant impact on survival, selection of healthier or younger men with prostate cancer and a longer life expectancy than average who may benefit from early detection and treatment is desirable.

Prognostic factors, pre- and post-treatment:

In the population of screened men of the present study 30 of 101 men treated by radical prostatectomy in our institution (30%) have tumors that may qualify as clinically unimportant if a worst case scenario is applied: no Gleason pattern 4 or higher and pathologic locally confined disease. A detailed analysis is subject of a separate report [17]. Only 7 of these 30 men were older than 64 years and 13 were younger than 60 years. This indicates that the majority of these men may have benefited from the early detection of their tumors since they are relatively young and the time during which the tumor could have progressed is long. Unfortunately it is impossible to determine at the time of diagnosis which patients will benefit from early detection and treatment. The clinical and pathological features of the cancers detected in ERSPC Rotterdam show a poor correlation. The prediction of extracapsular disease through DRE and TRUS is not reliable. Clinical and pathological findings concerning capsular penetration appear to be unrelated ($p=0.76$, chi square). In about 30% of tumors capsular penetration is not recognized at clinical examination. The grade of differentiation in the radical prostatectomy specimen are underestimated by the grade in the biopsy specimen ($p<0.001$, wilcoxon paired rank). The biopsy MD Anderson grade and the grade in the radical prostatectomy specimen were equal in 70% of cases. The biopsy Gleason scores and the Gleason score in the radical prostatectomy specimen were equal in 46% of cases. The relevance of this finding however, remains questionable since a well-differentiated biopsy outcome does not guarantee a well-differentiated tumor. In 22% of radical prostatectomy specimens the MD Anderson grade is underestimated by the biopsy results. The Gleason score of the radical prostatectomy specimen was underestimated in 39% of cases. This tendency to undergrade as well as the fact that the frequency and percent of poorly differentiated carcinoma in the biopsies was less than in the radical prostatectomies has been well documented [18, 19]. In our series, there were 13 cases (8%) in which the radical prostatectomy specimen showed a poorly differentiated tumor whereas the biopsy grade was well or moderately differentiated. All but one were clinically localized whereas the pathological stage showed extracapsular disease in 10 (77%) cases. Six patients (46%) had T4 disease. The PSA value at the time of diagnosis was between 4 and 10 ng./ml. in 10 of these patients, three men had a PSA value greater than 10 ng./ml.. The features of these cases are very unfavorable and could not have been anticipated based on clinical stage, grade and PSA level.

Thirty percent of these specimens showed positive margins, which is comparable with the overall percentage of positive margins. Whether these patients have been cured will have to be concluded from their follow-up results. Eventually if screening for prostate cancer ever becomes a health care policy, test procedures must become more selective. Those tumors, which are aggressive and curable, must be identified prior to decision making. Treatment and even biopsy in men with a low risk on progressive disease must become avoidable.

PSA and tumor characteristics:

The overall stage distribution shows 66% of cancers treated by radical prostatectomy are organ confined. At PSA levels below 4 ng./ml. 84% of cancers are organ-confined whereas 16% show extracapsular growth. Capsular penetration and PSA level are related ($p<0.001$, chi-square). Prostate cancer detected at PSA levels below 4 ng./ml. has a more favorable grade distribution. We found a statistically significant positive correlation between the serum PSA value and the grade of differentiation in the radical prostatectomy specimen. In our series no poorly differentiated tumors were diagnosed at PSA levels below 4 ng./ml.. Moreover, 77% of these cancers were well differentiated. At PSA levels below 4 ng./ml. 20% of positive margins were seen versus 31% of positive margins in tumors detected at PSA levels above the threshold value. This difference was not significant ($p = 0.14$, chi-square). It can be concluded though that prostate cancer detected under a PSA threshold level of 4 ng./ml. shows more favorable characteristics than prostate cancer detected above this threshold. Whether these cancers form a window of opportunity for curative treatment and mortality reduction or add to the pool of insignificant prostate cancer will have to be determined after comparison of the screening and control group at the endpoint of this study. The fact however, that part of these tumors show capsular penetration and a moderate grade of differentiation (more than 50% Gleason score 7) suggests that this subset as a whole should not be considered insignificant at this time.

T1C cancers are significantly more often organ confined (70%) than palpable or visible cancers (51%) detected at PSA levels ≥4 ng./ml. ($p = 0.03$, chi square). The grade distribution shows an identical grade distribution for T1C and not T1C cancers. Both categories show 14% of poorly differentiated tumors and approximately 40% are moderately differentiated. Positive margins were seen in 28% of all prostatectomies. The T1C cancers showed 26% of positive margins versus 34% in not T1C cancers, this difference however was not statistically significant ($p = 0.36$, chi square). This suggests

that T1C cancers are not much different from palpable and visible cancers in terms of grade and positive margins, however, these tumors are more often locally confined. There was no statistically significant difference between palpable and impalpable disease at PSA levels of 4 ng./ml. or higher. Palpable disease was pathologically confined in 53% of cases whereas 63% of impalpable cases were organ confined (p=0.27, chi square). There were no statistically significant differences in grade of differentiation and positive margins.

To date there have been only few investigations on the pathological characteristics of prostate cancer detected through screening of the general population [7, 20, 21]. The pathological characteristics of cancers detected in the ERSPC section Rotterdam are comparable to the characteristics of other screening programs that have been described previously as can be appreciated in Table 7.

Most cancers are confined to the prostate (66%) and lymphnode metastases are sporadically seen. In 72% of cases there is no indication for residual cancer after radical prostatectomy, however, the follow-up of patients with positive margins will show whether the treatment has been successful since it has been shown repeatedly that positive surgical margins do not inevitably lead to progression [22, 23].

	N	*Intracapsular disease*	*Seminal vesicle invasion*	*Positive margins*	*Lymph node metastases*
Humphrey [7]	100	61%	4%	34%	1%
Smith [20]	816	71%	6%	/	2.1%
Mettlin [21]	100	64%	/	/	6%
Present study	*172*	*66%*	*4%*	*27%*	*1%*

Table 7:
pathological characteristics of screen detected prostate cancer treated by radical prostatectomy. Comparison with series from literature.

Conclusion:

Comparison of the characteristics of prostate cancer detected through screening of the general population with the features of incident cases of prostate cancer in a population based cohort of men where no organized screening for the disease took place shows a dramatic stage reduction mainly expressed in the proportion of metastasized cases. Whether this stage reduction will lead to a decrease in disease specific mortality remains unknown since the effect of lead time and length time bias are unknown. A definitive conclusion will not be possible until the endpoint of the study is reached and the disease specific mortality within the screened and the control group will be compared. In the meantime the study of features that may allow screening to become more selective should have high priority.

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Chapter VIII

General discussion*.

The incidence of prostate cancer in the Netherlands in the year 1994 [1] amounts to 6,315 men at a crude rate of 83.0 per 100,000 person years. The cumulative risk to be diagnosed with prostate cancer from the age of 55 until death is 9.9 %. In 1994 prostate cancer represented 19 % of all new cancers diagnosed in males. The mortality from prostate cancer amounts to 2,374 men at a crude rate of 31.2 per 100,000 person years. These figures indicate that prostate cancer is an important health issue. The incidence of prostate cancer in the Netherlands is rising. Since 1989 there has been a 51% increase in absolute numbers and a 40 % increase in crude rate. This increase was mainly seen in localized disease but advanced disease also showed a moderate increase. The age adjusted mortality showed an increase of 7 % since 1989 and 20 % since 1980. This increase however was less than the increase in incidence. Two mechanisms may explain this discrepancy: First of all increased testing may lead to increased diagnosis of clinically not apparent prostate cancer at an earlier stage (stage reduction). Furthermore, progress in treatment of localized prostate cancer could explain the discrepancy between incidence and mortality. This however, will have to be concluded from randomized trials with prostate cancer mortality as a main outcome.

The dilemma whether or not to perform prostate cancer screening has important implications for both individual and public health but no randomized trial has ever demonstrated or refuted the benefit of prostate cancer screening. Furthermore, if screening for prostate cancer should be able to reduce the disease specific mortality, the overall balance of benefit and harm of both diagnostic procedures and treatment of the disease is unclear.

Performance of screening tests

It is generally accepted that PSA is the strongest indicator for prostate cancer. Because it might be unethical for researchers to perform biopsies on men with normal PSA values the true sensitivity and specificity of PSA screening is unknown. In early studies a PSA

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* *Prostate cancer screening and characteristics of prostate cancers detected. JBW Rietbergen and FH Schröder. European Urology Update Series 1998; (in press).*

cut-off value of 4 ng./ml. was arbitrarily chosen [2]. Labrie and associates [3] have made an effort to redefine the cut-off level using a ROC curve analysis. They conclude that a PSA cut-off level of 3 ng./ml. is a more suitable cut-off level above which further testing should take place. However, in most case finding and screening studies biopsies are performed at PSA levels of 4 ng./ml. or higher [4-9]. At PSA levels below this threshold level biopsies were taken if DRE findings were abnormal and in some studies TRUS was added as a screening tool. The percentage of the male population with a PSA level of 4 ng./ml. or greater lies between 11% and 15% and in this subset of men about 75% of prostate cancer cases are diagnosed. In the cited papers it is concluded that DRE and/or TRUS have a limited additional value in prostate cancer detection. In our evaluation of PSA, DRE and TRUS in a population based prostate cancer screening program (*Chapter II*) serum PSA proved to be the most powerful predictor for a positive biopsy. The evaluation was done on 4,344 consecutively screened men of whom 981 were biopsied and 170 cases of prostate cancer were detected. Overall PSA correctly predicted the outcome in 77% of biopsied men. The use of DRE or TRUS would have increased this percentage to 79%. The use of the combined screening tests showed a predictor value of 80% within the biopsied population. This indicates that DRE and or TRUS are of limited additional value. At PSA levels below the threshold level of 4 ng./ml. DRE and TRUS were responsible for 49.2% of biopsy indications and the detection of 19.8% of all cancers diagnosed in 86.6% of all screened men. These cancers would have been missed if serum PSA alone was used as the only screening test. The number of biopsy indications, men screened and cancers detected were evaluated in relation to the serum PSA value in an attempt to find a PSA value with optimal efficacy i.e. a PSA value where not performing biopsies would save a maximal amount of biopsy procedures per cancer not detected. This optimal balance between biopsies saved and cancers lost was reached at a PSA level of 1.7 ng./ml.. In a later evaluation on 7,775 screened men the optimal PSA value appeared to be between 1.6 ng./ml. and 2.4 ng./ml.. This indicates that the performance of DRE and TRUS are dependent of the PSA value and that performing biopsies indicated by DRE and/or TRUS starts to be efficient from a PSA level of approximately 2 ng./ml. or higher.

Improvement of specificity in PSA based screening

Improvement of the specificity of the screening procedure is an important issue in prostate cancer screening. Several conditions of the prostate as benign prostate hyperplasia (BPH), acute prostatitis, prostatic ischemia and other forms of prostatic perturbation have been shown to increase the serum PSA value [10-12].
Several methods have been suggested to reduce the number of false positive biopsy indications. Oesterling and associates suggested the use of Age Specific reference ranges for PSA [13] based on the observation that older men have higher serum PSA values. The relation between gland volume and the PSA value [14,15] has led to the concept of PSA corrected for prostate volume or PSA density (PSA-D). Benson and coworkers showed that PSA-D discriminates better between patients with prostate cancer and BPH than PSA alone [16]. This was opposed by several authors who did not find an advantageous effect of the use of PSA-D [17,18] or felt that too many cases of prostate cancer are being missed if PSA-D is used [19,20]. In chapter II, age specific reference ranges were retrospectively applied to the population under study. The results however were not very promising. Saving 14.3% of biopsies would leave 12.9% of cancers undetected. The use of PSA-D at a cutoff level of 0.1 ng./ml./cc would save the same percentage of biopsies at the cost of 7.6 % of cancers remaining undetected. The use of prostate volume as an extra parameter in predicting the biopsy outcome further increased the predictor value from 80% to 84% whereas age as additional parameter did not improve the predictor value at all. It is very likely that the use of age-specific reference ranges increases the sensitivity in younger men and decreases the biopsy rate in older men who may not be candidates for aggressive treatment [21] but does not change the overall specificity.
The use of the transition zone volume instead of total prostate volume was advocated by several groups [22,23]. They found a better performance of PSA corrected for transition zone volume (PSA-T) in predicting a positive biopsy. This however was opposed by Gohji et al. who found no advantage of the use of PSA-T over PSA-D [24]. Maeda and coworkers [25] found a better discriminatory potential between benign and malignant cases for PSA-T when compared to PSA-D. This difference however was not significant. These evaluations however, were not done on a population based screening cohort.
In the European Randomized Study of Screening for Prostate Cancer section Rotterdam the application of PSA corrected for total prostate volume and transition zone volume

was further elaborated in a ROC curve analysis of 1,202 men, biopsied because of a PSA level greater than or equal to 4 ng./ml.. The results are described in chapter IV. Of these men 361 had prostate cancer. PSA-D and PSA-T both showed a significantly better performance in discriminating benign cases from cancer cases than PSA alone. The performance of PSA-T was slightly better than PSA-D but the difference was not statistically significant. The use of a PSA-D threshold level of 0.12 ng./ml./cc would have saved 42% of biopsies and 17.7% of cancers would not have been diagnosed. A PSA-T cut-off value of 0.20 ng./ml./cc would have saved 41.8% of biopsies at the cost of 18.6% of cancers remaining undetected. We concluded that PSA-T offers no advantage over PSA-D and the use of PSA-D in prostate cancer screening does offer an increase in specificity but a decrease in sensitivity is inevitable. To what extent this is acceptable can only be concluded when proof concerning the benefit of prostate cancer screening is available and the characteristics and prognostic impact of missed cancers becomes known.

Stenman and associates showed that patients with prostate cancer have a significantly higher proportion of complexed PSA (a complex of PSA and α_1-antichymotripsin) than those with BPH [26]. Thus men with a relatively high free PSA or high free-to-total ratio are more likely to have benign disease. This was confirmed by Catalona and coworkers [27]. The use of the free-to-total PSA value in prostate cancer screening however is still under discussion [28-30]. In a comparing study of PSA and free-to-total PSA by Bangma et al. [31] in a population based screening population it was shown that the specificity might be improved minimally by the free-to-total PSA ratio, but not significantly in a sample of 1726 screened men. In a subsequent study (*Chapter III*) on 4800 screened men the free-to-total PSA ratio significantly decreased the number of biopsies by 40 % with a decrease in cancer detection of 12%. The result of application of the free-to-total ratio combined with DRE however, was identical to that of PSA-D in combination with DRE. The main advantage of application of the free-to-total PSA ratio above PSA-D lies mainly in the fact that time consuming and expensive ultrasonographic measurement of the prostate volume can be omitted.

Trans Rectal Ultrasound guided systematic sextant biopsy procedure

The cornerstone of prostate cancer diagnosis is the prostate biopsy procedure. This diagnostic tool is unfortunately the procedure with the highest risk of morbidity within the screening course. Hematuria and hematospermia are frequently seen, fever occurs in 2.5 to 6% of biopsied men [32-38] in spite of the use of antibiotics as prophylaxis. Even mortality has been reported [39]. In chapter V, 1,687 men are evaluated that underwent a sextant biopsy under antimicrobial prophylaxis mild complications as hematuria and hematospermia were seen in respectively 24 % and 45 % of cases. More severe complications were rarely seen. Fever was reported in 4.2% of cases, 3.1 % of biopsied men needed additional antibiotics. Hospitalization was necessary in 0.4% of cases and sepsis occurred in 0.2 % of biopsied men. These figures compared favorably to the reported complications in literature. Critical assessment of the biopsy procedure and the antimicrobial prophylaxis however, remains an important issue to reduce infectious complications. In our study potential risk factors as diabetes mellitus and previous episodes of prostatitis were not significantly associated with such complications whereas Aus and coworkers [35] observed a significantly higher number of infectious complications in patients with these risk factors. In our institution a randomized trial is on its way to investigate the ability of alternative antibiotics and dosage schemes to reduce the number of infectious complications.

A further point of interest concerning the systematic sextant biopsy procedure is the sensitivity of the procedure. Hodge and associates introduced the concept of systematic sextant biopsies and showed this method to be superior when compared to directed biopsies only [40]. Stamey suggested that directing the biopsies more laterally in the peripheral zone could further improve the yield of the biopsy procedure [41]. It has been well recognized that cases of prostate cancer are missed at the time of biopsy [42,43]. Keetch et al. demonstrated that after repeat biopsy of men with initially negative biopsies and a persistently elevated serum PSA 19% had cancer on biopsy [44]. In chapter VI, we investigated the yield of a repeat biopsy procedure after one year in men with initially negative biopsies and a persistently elevated serum PSA (greater than or equal to 4 ng./ml.) or abnormal findings at DRE and/or TRUS and normal serum PSA values. In 442 biopsied men 11% of prostate cancer cases were diagnosed. At elevated PSA levels, this figure was 11.6%. The tumor characteristics were not significantly different from cancers detected in the first round of screening. The only significant difference was the

higher prostate volume measured in the initial screening visit in the repeat biopsy group which explains why these cancers were not found in the first biopsy procedure. This confirms findings by Uzzo et al. [45]. Furthermore biopsy of additional areas may further improve the sensitivity of the biopsy procedure especially in men with larger prostates. Computer model based analysis showed that repeat biopsies would reliably detect 73% of previously detected cancers. A 10-core biopsy scheme would increase the yield to 96% [46]. There is evidence that such increased detection rates are clinically achievable. Eskew et al. reported on a 5 region biopsy technique and observed a 35% increase in detection rate when compared to the systematic sextant biopsy procedure. Whether increased sensitivity will lead to an improved prostate cancer specific survival remains a debated issue.

Characteristics of prostate cancer detected in population based screening

At the time of diagnosis, prostate cancer has often spread beyond the prostate. A descriptive study of prostate cancer incidence in the Amsterdam region of the Netherlands by Visser and Horenblas [47] showed that 31% of cases are not organ confined at the time of diagnosis and metastases are seen in 24% of newly diagnosed patients. The prognosis of locally advanced and advanced disease is poor; therefore the goal of early detection regimes is to diagnose prostate cancer at an earlier stage of its development in which treatment might be more successful.
Before the PSA era Chodak et al. [48] studied DRE as a screening method for prostate cancer in a referred patient population. The detection percentage in 2,131 men was 1.5% after the first round of screening. Clinically localized disease was seen in 68% and 14% of men had metastatic disease. The authors concluded that this modest stage reduction did not justify the use of DRE in mass screening programs. Catalona and associates compared a PSA-based screening group with a group of men referred for prostate biopsy because of an abnormal DRE [49]. The percentage of both clinically and pathologically confined disease was significantly higher (nearly doubled) in the PSA-based screening group when compared to the group of referred men. In a subsequent case finding study [50] of 24,346 men screened by serum PSA, 96% had clinically localized disease. Bone metastases were seen in 1% of cases. In men treated by radical prostatectomy 69% had pathologically organ confined disease. In a Swedish study [51] using PSA with a threshold level of 10 ng./ml. as a biopsy indication, in combination with DRE and TRUS

under this threshold level, 65 cases of prostate cancer were detected in 1,780 men. Sixty one percent of these cancers were clinically organ confined.

The American Cancer Society National Prostate Cancer Detection Project [52] found 93% clinically confined cases of prostate cancer and 3.6% of metastatic cases mainly using DRE and TRUS. Elevated PSA levels not explained by BPH led to some biopsies. The results of the multi-center approach in the prostate cancer awareness week in the U.S.A. [53] showed 88.9% of clinically localized tumors and 11% of advanced disease. This case finding study was conducted in a multi-center setting. If an elevated PSA value could be explained by BPH no biopsy was performed. Furthermore, the DRE results were interpreted; abnormal but not suspicious DRE did not prompt a biopsy. Abnormal test results were not used as a standard indication for biopsy but merely an indication for further follow-up by TRUS, bone scan, computed tomography or prostatic biopsy. Furthermore the interpretation of the results of this study is hampered by the low percentage of reported follow-up for men with positive test results.

In a population based randomized and controlled prostate cancer detection program by Labrie and coworkers [54] the use of DRE, TRUS and serum PSA-D led to the diagnosis of 252 cancers in 7,350 men in the first round of screening. Organ confined disease was seen in 70% of cases, extracapsular disease and metastatic disease were seen in respectively 19% and 10.5% of cases. The characteristics of cancers diagnosed in the first round of screening in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) are described in chapter VII. The characteristics of these cancers compare favorably to those in the previously cited studies. At PSA levels of 4 ng./ml. or higher all men were evaluated by systematic sextant biopsies. At PSA levels below this threshold DRE and/or TRUS abnormalities prompted a sextant biopsy procedure. The clinical stage distribution shows 2% of metastasized disease (0.9% bone metastases and 0.9% lymphnode metastases). Seventy eight percent of patients had clinically organ-confined disease. Radical prostatectomy was performed in 38% of men. Of these men 66% had pathologically organ confined disease, which is fully comparable to the results of Humphrey et al. [55] and Mettlin et al.[56]. The question how many of the cancers diagnosed by early detection regimes are clinically significant remains a debated issue. Several hypotheses have been used to demonstrate clinical insignificance of tumor in the radical prostatectomy specimen: Focal and well differentiated tumor [49]; Tumor volume smaller than $0.5cm^3$ [57]; Tumor volume smaller than $0.5cm^3$ and confined to the prostate with a Gleason score less than 7 [58]; Tumor volume smaller

than 0.2cm^3 and confined to the prostate with a Gleason score less than 7 [59]. Most of these hypotheses are based on the pathologic features of prostate cancer found at autopsy or in cystoprostatectomy specimens (latent prostate cancer). It is estimated that between 10 and 20% of all cancers diagnosed at screening have pathologic features comparable to these latent cancers. Evaluation of 51 radical prostatectomies for prostate cancer detected in the ERSPC section Rotterdam [60] showed 6% of insignificant cancer according to the Epstein criteria [59] or 18% according to the Ohori criteria [58]. These however are very crude criteria that are based on circumstantial evidence and do not measure the biologic potential of a tumor. Answers concerning biologic behavior of tumors will have to come from the field of molecular biology rather than from morphometric studies of diagnosed tumors.

Although the percentage of metastasized cancers found by screening of the general population is very low (2% versus 24% in incident cases) it is still unknown whether screening for prostate cancer will reduce mortality. This stage reduction however, may appear favorable but does not prove that prostate cancer screening will decrease prostate cancer mortality. Two biases are associated with screening: Bias as a result of increased survival in the screened group due to detecting the tumor earlier without genuinely prolonging life (lead time bias) and bias due to detecting slower growing tumors, that would never have led to mortality due to prostate cancer, in the screened men (length time bias). A randomized controlled trial with prostate cancer mortality, as endpoint is needed to avoid these biases. Not only would this avoid selection bias, but also by using reduction of prostate cancer specific mortality as the measure of outcome rather than survival after diagnosis, lead and length time bias can be avoided.

To our opinion screening for prostate cancer should not be applied to the general population at this time. Large prospective randomized screening studies with prostate cancer specific mortality as main outcome are on their way but results are not expected to be available within the next ten years. Those men who wish to be screened should be fully informed about the risks and potential benefits.

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Summary and conclusions.

Chapter I reviews all issues fueling the prostate cancer screening debate. The incidence and mortality data show prostate cancer is an important health problem. An important subject however is the fact that more men die with rather than from prostate cancer. Thus, screening for this disease will also detect cancers that will not lead to mortality. The performance of the screening tests is discussed as well as methods to improve the discriminatory potential between benign and cancer cases in order to avoid unnecessary biopsy procedures. Identification of possible insignificant prostate cancer cases and prediction of stage and grade through the use of the outcome of screening tests does not yet provide a secure method to select patients for treatment. The efficacy and adverse effects of the treatment options: Watchful waiting, radiotherapy and radical prostatectomy are discussed. In theory screening for prostate cancer may reduce mortality. Prostate cancer mortality decreases in certain areas of the U.S.A.. Whether this is the result of early detection and treatment policies remains questionable. This has to be demonstrated first in randomized controlled studies with prostate cancer mortality as the major endpoint.

The performance and efficacy of the screening tests is further elaborated in chapter II. The use of serum PSA provides the highest discriminatory potential between benign cases and prostate cancer cases. The additional value use of DRE and TRUS is limited. The PSA level below 4 ng./ml. is important since 19.8% of all cancers detected in the screening program are detected in this PSA range. Of all screened men 86.6% of men have PSA levels below 4 ng./ml.. Roughly half of all biopsies are performed in men with a PSA level below 4 ng./ml.. To reduce the number of unnecessary biopsies most is to be gained within this PSA range. At PSA levels below 4 ng./ml. biopsies are indicated by DRE and/or TRUS. The percentage of biopsies taken is approximately 14%. This percentage does not change with an increasing PSA level in the range between 0.1 and 4 ng./ml.. The ratio of the number of biopsies taken and the number of cancers detected however decreases with an increasing PSA level again indicating that PSA is a better predictor of a positive biopsy outcome than DRE or TRUS. The efficacy of performing biopsies is maximal from a PSA value of 1.7 ng./ml.. Not performing biopsies under this PSA threshold would result in the optimal ratio between the percentage of cancers not diagnosed and percentage of biopsies saved.

In chapter **III** the use of the free-to-total PSA ratio to reduce the number of unnecessary biopsies in the PSA range between 4 and 10 ng./ml. is discussed. This method is compared to the use of PSA corrected for total prostate volume (PSA-D) in combination with DRE and the use of serum PSA alone or combined with DRE. The use of a Free-to-total PSA ratio with a cutoff of 0.2 or less would save 44% of biopsies at the cost of not detecting 19% of cancers. The use of a PSA-D cutoff of 0.12 ng./ml./cc or more in combination with DRE would lead to a 43% reduction of the number of biopsies at the cost of 14% of cancers remaining undetected.
The effect of both methods on the number of biopsies saved and cancers remaining undetected is similar. The disadvantage of the use of PSA-D however is that time consuming and expensive volume measurements using TRUS are necessary whereas the use of the free to total PSA ratio is more cost effective.

The use of total prostate volume and the volume of the transition zone for correction of the serum PSA value is discussed in chapter **IV**. The comparison of the use of PSA-D and PSA-T as screening tests leads to the conclusion that there is no significant difference in the area under the ROC curves. Both methods however perform significantly better than PSA alone. The use of PSA-D with a threshold level of 0.12 ng./ml./cc would lead to a 42% reduction of the number of biopsies and 18% of cancers would remain undetected. The use of PSA-T with a cutoff level of 0.20 ng./ml./cc would reduce the number of biopsies with 42% at the cost of an 18.6% reduction of cancers detected.
The method of volume measurement was assessed as well. The results of the planimetrically determined volume and the prolate ellipsoid method for volume measurement were compared to the volume of the radical prostatectomy specimen. Both methods correlated well. The agreement of the planimetrically determined volume was slightly better. The comparison of the use of PSA corrected for planimetric and prolate ellipsoid volume by means of a ROC curve analysis showed no significant difference. Thus both volume measurements may be used for correction of the PSA value.
Whether the loss of cancers detected in a screening program in order to improve specificity is affordable remains an unanswered question.

The safety of a screening program depends mainly on the safety of the biopsy procedure since this procedure is responsible for most complications. In chapter **V** the

complications of the TRUS guided systematic sextant biopsy procedure are described. Minor adverse effects as hematuria and hemospermia are frequently seen, in 24% and 45% respectively. Major complications as fever requiring antibiotic therapy is seen in 3% of cases. Hospitalization was necessary in 0.4% of cases and sepsis was rare with a prevalence of 0.18%. These figures compare favorably with complication rates reported in literature. This has led to the conclusion that the biopsy procedure as performed in this study is a safe method however research remains necessary for further reduction of these adverse effects.

Although the biopsy procedure is regarded as the "golden standard" for presence or absence of cancer in the prostate it is clear that cancers are missed by the systematic sextant biopsy procedure. In chapter **VI** the results of 442 men with an initial negative biopsy who were biopsied again after 1 year are described. A true positive biopsy percentage of 11% was found in these men, which was significantly lower than the 19.9% true positive biopsy rate in the initial screening. The pathological tumor characteristics of the tumors detected in the re-biopsy group were similar to those in the initial screening group. Reason for not having diagnosed these cancer in the initial biopsy was explained by the finding that the prostate volume of the men with cancer diagnosed in the re-screening visit was significantly larger (42.6 cc versus 34.9 cc ($p=0.003$)). If prostate cancer screening proves to be effective in reducing mortality efforts will have to be made to improve the sensitivity of the biopsy procedure in men with larger prostates.

The reduction of prostate cancer mortality by screening of the general population is based on the hypothesis that prostate cancer is diagnosed in an earlier stage in which it is more often confined to the prostate, which increases the chance of curative treatment. In Chapter **VII** the characteristics of the cancers diagnosed in the ERSPC section Rotterdam are described and compared to the characteristics of incident cancers diagnosed in the daily clinical routine in the Amsterdam region of the Netherlands. In the Amsterdam region 24% of cancers had already metastasized at the time of diagnosis whereas screen detected cancers were metastasized in 2% of cases. This however does not provide proof for the success of a screening program since a conclusion considering a beneficial effect of screening is hampered by length time and lead time bias. Such proof can only be provided by randomized controlled studies with prostate cancer specific mortality as major outcome.

Samenvatting en conclusies.

Hoofdstuk I geeft een overzicht van de problemen waarop de discussie omtrent bevolkingsonderzoek naar prostaatkanker is gebaseerd. De incidentie en mortaliteit getallen laten niet alleen zien dat prostaatkanker een belangrijke ziekte is maar ook dat meer mannen sterven met prostaatkanker dan aan deze ziekte. Een bevolkingsonderzoek zal niet alleen resulteren in de diagnose van prostaatcarcinomen die tot mortaliteit geleid zouden hebben maar ook in de diagnose van prostaatcarcinoom bij mannen welke zullen overlijden aan eventuele comorbiditeit. De eigenschappen van de onderzoeksmethoden worden beschouwd evenals de methoden die het onderscheidend vermogen tussen kanker en benigne gevallen van de betreffende onderzoeksmethoden kunnen vergroten om overbodige biopsieën te voorkomen. Identificatie van mogelijk onbelangrijke prostaatkanker gevallen en het voorspellen van maligniteitsgraad en het stadium met behulp van de resultaten van de onderzoeken is vooralsnog niet betrouwbaar als het gaat om het selecteren van de patiënten die al dan niet behandeld dienen te worden. De effectiviteit en nadelige effecten van de verschillende behandelingsmethoden: uitgestelde behandeling, bestraling en radicale prostatectomie worden besproken. Het is theoretisch mogelijk dat een bevolkingsonderzoek naar prostaatkanker de sterfte aan deze ziekte vermindert. De prostaatkanker sterfte daalt in een aantal gebieden in de Verenigde Staten, het is echter nog onduidelijk of dit het resultaat is van de daar toegepaste vroege opsporing en behandeling. Een gerandomiseerde studie met een controle groep en een screeningsgroep waarbij als eindpunt een reductie van prostaatkanker specifieke sterfte gehanteerd dient te worden zal hieromtrent uitsluitsel moeten geven.

In hoofdstuk II wordt dieper ingegaan op de eigenschappen en de effectiviteit van de verschillende onderzoeksmethoden. Het gebruik van de serumconcentratie van het prostaat specifiek antigen is de beste test voor vroege opsporing van prostaatkanker. Het onderscheidend vermogen tussen benigne en maligne is superieur ten opzichte van het gebruik van het rectaal toucher en transrectale echografie. De toegevoegde waarde van de laatstgenoemde onderzoeken is beperkt. Met name het gebied onder de PSA waarde van 4 ng./ml. is belangrijk aangezien in de beschreven screeningsstudie 19.8 % van alle prostaatkanker in dit gebied ontdekt worden. Van alle gescreende mannen heeft 86.6% een PSA waarde onder de 4 ng./ml. en grofweg de helft van alle biopsieën worden in

deze groep gedaan zodat de meeste winst betreffende de vermindering van onnodige biopsieën in deze groep te behalen is. Onder een PSA waarde van 4 ng./ml. worden alleen biopsieën genomen als er afwijkingen zijn bij het rectaal toucher en/of afwijkende echobevindingen. Het percentage gescreende mannen dat een biopsie ondergaat is ongeveer 14 %. Dit percentage is onafhankelijk van de PSA waarde in het PSA gebied onder de 4 ng./ml.. De verhouding tussen het aantal biopsieën en het aantal gediagnostiseerde kankers neemt echter af bij een toenemende PSA waarde. De effectiviteit van een biopsie is maximaal bij een PSA waarde van 1.7 ng./ml.. Het afzien van een biopsie onder deze waarde resulteert in een optimale verhouding tussen het percentage kanker dat gemist wordt en het percentage bespaarde biopsieën.

In hoofdstuk III wordt het gebruik van de verhouding tussen vrij en totaal PSA (F/T ratio) in een PSA gebied tussen 4 ng./ml. en 10 ng./ml. besproken teneinde de hoeveelheid overbodige biopsieën te verminderen. Deze methode wordt vergeleken met het gebruik van PSA gecorrigeerd voor het prostaatvolume (PSA-D) gecombineerd met rectaal toucher en het gebruik van PSA alleen met rectaal toucher. Het gebruik van de F/T ratio met een waarde van 0.2 of minder, vermindert het aantal biopsieën met 44% en reduceert de kanker detectie met 19 %. Het gebruik van PSA-D met een waarde van 0.12 ng./ml./cc of gerecombineerd met rectaal toucher levert een reductie van 43% van het aantal biopsieën op ten koste van 14% van de gediagnostiseerde kankers. Het effect van beide methoden op de biopsie-reductie en kankerdetectie is volledig vergelijkbaar. Het nadeel van het gebruik van PSA-D is echter de tijdrovende echografische volumemeting. De kosten effectiviteit ven het gebruik van de F/T ratio zal dan ook groter zijn.

Hoofdstuk IV is gewijd aan het gebruik van PSA gecorrigeerd voor het totale prostaatvolume (PSA-D) en het overgangszone volume (PSA-T) als test. Uit de in dat hoofdstuk beschreven vergelijking tussen beide methoden kan geconcludeerd worden dat er geen significant verschil is in het oppervlak onder de ROC-curve die de verhouding tussen sensitiviteit en specificiteit beschrijft. Beide methoden hebben wel betere test eigenschappen in vergelijking met het gebruik van PSA alleen. Wanneer PSA-D met een drempelwaarde van 0.12 ng./ml./cc wordt gebruikt levert dit een besparing op van 42 % van de biopsieën ten koste van 18 % vermindering van de kanker detectie. Het gebruik

van PSA-T met een drempelwaarde van 0.20 ng./ml./cc vermindert het aantal biopsieën met 42 % ten koste van 18.6 % van de voorheen wel gedetecteerde carcinomen.
In dit hoofdstuk wordt ook de methode van volumebepaling onderzocht. De resultaten van het planometrisch vastgestelde volume en de volumina bepaald met behulp van de volgende formule: 0.52 maal de gemeten lengte maal breedte maal hoogte van de prostaat wordt vergeleken met het volume van het resectiepreparaat na radicale prostatectomie. Beide echografische methoden laten een goede correlatie zien met het eigenlijke prostaatvolume. Het planometrisch bepaalde volume stemt echter iets beter overeen met het eigenlijke prostaatvolume. Een vergelijking van beide methoden door middel van een ROC curve analyse laat geen significant verschil zien. Beide volume metingen kunnen gebruikt worden voor de correctie van PSA voor prostaatvolume.
De vraag of het niet diagnostiseren van prostaatcarcinomen teneinde de specificiteit van een bevolkingsonderzoek te verbeteren consequenties heeft blijft vooralsnog onbeantwoord.

De veiligheid van een bevolkingsonderzoek naar prostaatkanker is met name afhankelijk van de veiligheid van de biopsie procedure aangezien hierbij de grootste kans op complicaties bestaat. In hoofdstuk V worden de complicaties van de systematische sextant biopsie procedure beschreven. Minder ernstige nadelige effecten als hematurie en hemospermie worden frequent gezien in respectievelijk 24 % en 45 % van de gevallen. Meer ernstige nadelige effecten als infectie en koorts, behandeld met antibiotica, werd in 3% van de gevallen gezien. Opname in het ziekenhuis was noodzakelijk in 0.4% van de gevallen. Sepsis was zeldzaam en werd in 0.18 % van de gebiopteerde mannen gezien. Deze aantallen steken gunstig af in vergelijking met de getallen in de geraadpleegde literatuur. Hieruit concludeerden wij dat de biopsie-procedure zoals uitgevoerd in het kader van onze studie een veilige methode is. Het is echter wel noodzakelijk verder onderzoek te doen om de nadelige gevolgen van de biopsie procedure te verminderen.

De biopsie procedure geldt als "gouden standaard" voor het al dan niet aanwezig zijn van een prostaatcarcinoom. Het is echter duidelijk dat er kankers gemist worden. In hoofdstuk VI worden de resultaten van een her-biopsie bij 442 het jaar daaraan voorafgaand gebiopteerde mannen beschreven. Het percentage juist positieve biopsie indicaties was 11 % in deze groep, hetgeen significant lager is dan de 19.9 % in de initieel gebiopteerde groep. De pathologische tumor eigenschappen van de in de her-biopsie

gediagnostiseerde tumoren zijn vergelijkbaar met de karakteristieken in de initieel gescreende groep. Het feit dat de tumoren uit de her-biopsie groep niet in de initiële screening ontdekt zijn wordt verklaard door de bevinding dat de prostaatvolumina in deze groep op het moment van de initiële screening significant groter waren (42.6 cc versus 34.9 cc (p=0.003)). Dit betekent dat verdere verbetering van de gevoeligheid van de biopsie-procedure noodzakelijk is bij mannen met een groot prostaatvolume, echter alleen wanneer een bevolkingsonderzoek naar prostaatkanker een positief effect op de mortaliteit blijkt te hebben.

De vermindering van sterfte aan prostaatkanker door bevolkingsonderzoek is gebaseerd op de hypothese dat de carcinomen in een vroeger stadium van hun ontwikkeling gediagnostiseerd worden waarin de ziekte frequenter tot het orgaan beperkt blijft, hetgeen de kans op curatief zijn van de behandeling vergroot. In hoofdstuk VIII worden de karakteristieken van de in de Rotterdamse onderzoeksgroep gediagnostiseerde carcinomen beschreven. Er wordt een vergelijking gemaakt met de karakteristieken van de in de dagelijkse klinische routine gediagnostiseerde tumoren uit de regio Amsterdam. In de laatstgenoemde regio bleek 24% van de tumoren reeds gemetastaseerd op het moment van diagnose. In de gescreende groep uit Rotterdam bleek in 2 % van de gevallen sprake van metastasen. Deze bevinding is echter niet bewijzend voor de effectiviteit van een bevolkingsonderzoek. Enerzijds kan het zo zijn dat het beloop van de ziekte identiek is maar dat alleen de tijdsduur waarin de patiënt op de hoogte is van zijn maligniteit verlengd is (lead time bias). Anderzijds kan het zijn dat het beschreven effect het gevolg is van de diagnose van kleine ongevaarlijke vormen van prostaatkanker met een gunstige prognose die de poel van potentieel gevaarlijke carcinomen slechts verdunnen waardoor het aanvankelijk lijkt of er over het algemeen een gunstiger stadium wordt gediagnostiseerd maar het uiteindelijke beloop in de gehele groep ongewijzigd blijft (length time bias). Bewijs voor een gunstig effect van bevolkingsonderzoek naar prostaatkanker kan alleen geleverd worden na een gerandomiseerd onderzoek met een screening en controle groep waarin een verschil in prostaatkanker sterfte tussen beide groepen uiteindelijk uitsluitsel geeft.

Curriculum Vitae

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1976-1983	VWO, Christelijk Lyceum, Alphen aan den Rijn
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