EARLY DIAGNOSIS OF PROSTATE CANCER IN THE WESTERN CAPE

C F Heyns, A M Naudé, A J Visser, D C Marais, H B Stopforth, J K Nyarko, G A Stellmacher

Background. Early stage prostate cancer does not cause symptoms, and even metastatic disease may exist for years without causing symptoms or signs. Whereas early stage prostate cancer can be cured with radical prostatectomy or radiotherapy, the prognosis of patients with locally advanced or metastatic cancer is significantly poorer.

Objectives. In view of the high incidence of advanced and therefore incurable prostate cancer seen at the oncology clinic of the Department of Urology, Tygerberg Hospital, we started a prostate clinic with the aim of detecting early stage prostate cancer which is potentially curable. A secondary objective was to investigate the question whether there is a higher incidence of prostate cancer among black African men.

Patients and methods. Men aged 50 - 70 years were invited by means of media communications (newspaper and radio) to attend our prostate clinic for a free physical examination, including a digital rectal examination (DRE) and serum prostate specific antigen (PSA) assay. If the DRE was clinically suspicious of malignancy and/or the serum PSA was > 4 ng/ml, the patient was appropriately counselled and referred for transrectal ultrasound (TRUS)-guided sextant prostate biopsy.

Results. In the period June 1997 - September 1999 a total of 1 056 men attended the prostate clinic. Biopsies were indicated in 160 cases, and were obtained in 114 (71.3%, i.e. 10.8% of the entire cohort). Prostate cancer was detected on first biopsy in 3.5% of the entire group of men (in 35.9% of those with a clinically abnormal DRE, in 41.3% of those with a serum PSA > 4 ng/ml and in 88.6% of those with an abnormal DRE and serum PSA > 4 ng/ml. In the 37 men with prostate cancer, the clinical tumour stage was T1 - 2 in 83.8% and T3 - 4 in 16.2%. In the group of patients with clinical stage T1 - 2 tumours, the treatment was watchful

waiting in 62.5% of cases, radiotherapy in 20.8% and radical prostatectomy in 16.7%. Analysis of the data according to race showed that in the group of 47 black men there was a higher percentage of clinically abnormal DRE, PSA > 4.0 ng/ml and biopsies showing malignancy, and a higher overall prostate cancer detection rate (8.5%).

Conclusions. Our prostate cancer detection rate of 3.5% is slightly lower than that reported in larger studies (4.7%), which may be due to the fact that prostate biopsy was performed in only 71% of those who had an indication for biopsy. In the men diagnosed with clinically localised prostate cancer, potentially curative treatment was given in only 37.5% of cases. This compares unfavourably with the historical cohort of men seen at our oncology clinic, where 53% received potentially curative treatment, and a large European study where potentially curative treatment was given in 89% of cases. Our finding that black men had a higher percentage of clinically abnormal DRE, PSA > 4.0 ng/ml and biopsies showing malignancy and a higher overall detection rate of prostate cancer should be interpreted with caution, since black men comprised only 4.5% of our overall study cohort.

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Department of Urology, University of Stellenbosch and Tygerberg Hospital, Tygerberg, W Cape

C F Heyns, MB ChB, MMed (Urol), PhD, FCSSA (Urol)
A M Naudé, MB ChB
A J Visser, MB ChB
D C Marais, MB ChB
H B Stopforth, MB ChB
J K Nyarko, MB ChB
G A Stellmacher, MB ChB

Prostate cancer is the second most common histologically diagnosed cancer in South African men, with an estimated annual incidence of 19.1 per 100 000 men.[1] However, this incidence rate is probably deceptively low owing to incomplete reporting of cases. Comparison of the incidence of prostate cancer in the different racial groups shows that it is the second most common histologically diagnosed malignancy in whites, blacks and coloureds, and the fourth most common malignancy in Asian (Indian) men in South Africa.[1] There have been several studies suggesting that black (African) men may have a higher incidence and a more aggressive type of prostate cancer, but there are no published data from South Africa addressing these questions.[2,3]

Early stage prostate cancer does not cause symptoms, and even metastatic disease may exist for years without causing symptoms or signs. Whereas early stage (localised or intracapsular) prostate cancer can be cured with radical prostatectomy or radiotherapy, the prognosis for patients with locally advanced (extracapsular) cancer is significantly poorer. Once metastases have occurred, the disease is no longer curable and the median survival is in the range of 180 weeks, despite the fact that approximately 80% of patients initially respond well to endocrine treatment (androgen ablation).[4]

Two factors are highly predictive of survival in patients with localised prostate cancer treated conservatively, namely tumour histological features (especially grade), and patient co-

morbidity.[5] Therefore, healthier men with a longer life expectancy (around 10 years) may benefit from early detection and treatment. The incidence of prostate cancer in the USA has risen dramatically, which is mainly explained by the increased awareness and early detection activities.[6] Recently, declines in the incidence have been reported.[7] Furthermore, a decrease in prostate cancer mortality in the USA has been observed, and although there has been no clear explanation for this phenomenon, the possibility that this trend is the result of early detection and treatment cannot be excluded.[8]

BACKGROUND

In the period 1976 - 1996, a total of 1 749 men with histologically confirmed adenocarcinoma of the prostate were seen at the oncology clinic of the Department of Urology at Tygerberg Hospital.[9] Virtually all of these patients presented because of symptoms related to prostatic disease. The majority (77%) were between 61 and 80 years of age, with 51% over 70 years old. The race distribution was 51% coloured and Asian, 44% white and 5% black, compared with the race distribution of the South African population as a whole, which comprises approximately 69% black, 18% white, 11% coloured and 4% Asian (Indian). This reflects the referral pattern to our hospital over the past 20 years, and does not imply that prostate cancer is less common in black men. However, it is not possible to calculate accurately the incidence rate of prostate cancer in the Western Cape since the denominator (total population of our referral area) is not accurately known.

The tumour stage in the 1 749 men with prostate cancer seen at our hospital between 1976 and 1996 was clinically localised (T1 - 2) in 34% of cases, and locally advanced in 64% (T3 in 24% and T4 in 42%).[9] Localised tumours were more common in white patients, while locally advanced tumours were more common in coloured and black patients. Bone metastases demonstrated by radio-isotope scintigraphy were present in 45% of the patients at presentation.[9] This is similar to the situation in the USA in 1982, before the era of screening, when more than 40% of prostate cancer at the time of diagnosis was locally advanced or metastatic.[10] Even in a more recent survey (1989 - 1994) carried out in the Netherlands during the era of screening, it was found that among patients who presented because of symptoms, 24% had metastases at the time of diagnosis and 8% had locally advanced cancer.[11]

The initial treatment in the cohort of 1 749 patients seen at our oncology clinic was hormonal (mostly bilateral orchidectomy) in 62%, radiotherapy in 21%, watchful waiting (observational follow-up) in 16% and radical prostatectomy in 1%.[9] Patients who could be considered potential candidates for curative treatment (stage T1b - 2 M0 tumours, patient under 70 years old) comprised only 13% of the entire cohort, since 66% were stage T3 - 4 tumours and a further 21% were stage T1a or

M1 or patients over 70 years old. In those with potentially curable disease (stage T1b - 2 M0, age under 70 years), the primary treatment was radiotherapy in 42%, watchful waiting in 39%, radical prostatectomy in 11% and hormonal (androgen ablation) in 8% (Department of Urology, Tygerberg Hospital — unpublished data, 1998).

Early detection of prostate cancer is possible, largely owing to the identification of serum prostate-specific antigen (PSA), which has proved to be the most powerful tool available for an early diagnosis of prostate cancer.[12] In most studies the upper limit of normal is accepted as 4.0 ng/ml, although some authors have suggested that a lower cut-off level of 3.0 ng/ml should be used.[12-16] Despite considerable inter-examiner variability in the detection of prostate cancer by digital rectal examination (DRE), the latter nonetheless significantly increases the detection rate that can be achieved with PSA alone.[17] Transrectal ultrasound (TRUS)-guided systematic sextant (six core) biopsy of the prostate significantly increases the ability to detect early prostate cancer, since it is superior to random biopsies, even though the chance of missing tumour is approximately 27%.[18,19]

Data from large-scale randomised clinical trials of screening for prostate cancer have shown that the screening tests are generally well accepted, that 95% of all participants are willing to be re-screened, and that TRUS-guided systematic sextant biopsy of the prostate is a safe procedure for the diagnosis of prostate cancer within the general population.[20]

OBJECTIVES

In view of the high incidence of advanced and therefore incurable prostate cancer seen at our oncology clinic, we started a prostate clinic in June 1997 with the aim of detecting early stage prostate cancer which is potentially curable. A secondary objective was to compare the prostate cancer detection rates between race groups to address the question of whether there is a higher incidence among black African men.

PATIENTS AND METHODS

Men were invited by means of media communications (newspaper and radio) to attend the prostate clinic at the Department of Urology, Tygerberg Hospital for a free physical examination including a DRE and serum PSA assay. The target group was asymptomatic men aged 50 - 70 years. The men were seen by a registrar in urology and the assessment consisted of the following: international prostate symptom score (IPSS), urine dipstix analysis, blood taken for serum PSA (Abbott IMX assay),[21] full medical history and physical examination, including blood pressure and DRE. If the DRE was clinically suspicious of malignancy and/or the serum PSA was > 4 ng/ml, the patient was appropriately counselled and

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referred for TRUS-guided sextant prostate biopsy. Patients were given the options of having the biopsy performed at Tygerberg Hospital or being referred to a private practising urologist of their choice.

Biopsies were performed in an outpatient setting without prior bowel preparation or cleansing enemas and without anaesthesia. Aspirin or anticoagulant therapy was stopped 10 days before the biopsy, after consultation with the subscribing physician. Two hours before and 4 hours after the biopsy all patients received oral antimicrobial therapy, usually amoxycillin-clavulanic acid, ofloxacin or ciprofloxacin. TRUS was performed using a 7 MHz-biplanar endorectal transducer. Systematic sextant biopsies (six cores) were taken during longitudinal scanning through an oblique channel in the ultrasound probe using a Biopty or Magnum biopsy gun and an 18-gauge (1.2 mm) biopsy needle. If a suspicious (hypo-echoic) lesion was seen on TRUS, a biopsy was done through the lesion.[20]

Statistics

The patient data were recorded prospectively on a custom-designed computer database (Access) and analysed with statistical software available on Excel.

Ethics

Prior approval for the study was obtained from the Ethical Committee of the Faculty of Medicine, University of Stellenbosch.

RESULTS

During the period June 1997 to September 1999 a total of 1 056 men attended the prostate clinic. Their median age was 60.6 years, and only 11% were older than 70 years (Fig. 1). The mean and median IPSSs were 10 and 8, respectively. The IPSS was ≤ 5 in 38% of cases and 6 - 10 in 24%, therefore 62% of the men had an IPSS ≤ 10, indicating that the majority of patients were relatively asymptomatic (Fig. 2). The race distribution was 623 (59.5%) white, 337 (32.3%) coloured, 47 (4.5%) black and 40 (3.8%) Asian.

The findings with regard to DRE, serum PSA and TRUS-guided prostate biopsy are given in Table I. Approximately three biopsies were required to diagnose one prostate cancer. The prostate biopsy results in subgroups of men are given in Table II.

In patients with histologically diagnosed benign prostate hyperplasia (BPH), the mean free/total PSA ratio was 0.24, median 0.20 and range 0.03 - 0.59, whereas in men with histologically confirmed prostate cancer the mean free/total PSA ratio was 0.17, median 0.15 and range 0 - 0.43. The difference was statistically significant ($P = 0.012$, Student's t-test).
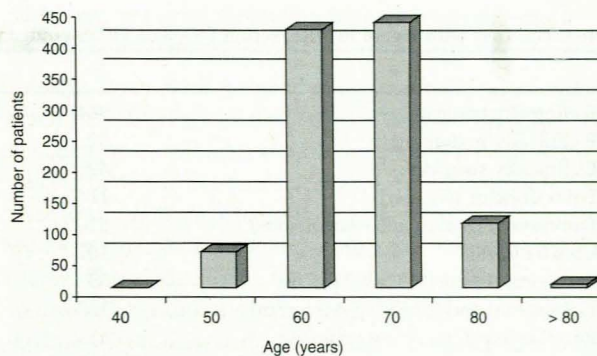

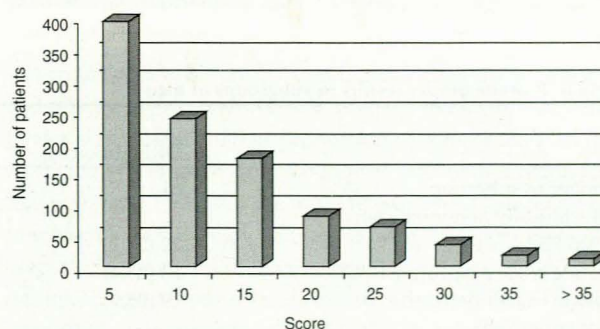Fig. 1. Age distribution of men attending the prostate clinic.

Fig. 2. International Prostate Symptom Score (IPSS) for men attending the prostate clinic.

In the 37 men with histologically confirmed prostate cancer, the clinical tumour stage was T1 - 2 in 31 (83.8%) and T3 - 4 in 6 (16.2%). The treatment for 27 men (unknown in 10 patients) was observational follow-up (watchful waiting) in 16 cases (59.3%), radical prostatectomy in 5 (18.5%), radiotherapy in 5 (18.5%) and hormonal treatment in 1 (3.7%). In the group of 24 patients with clinical stage T1 - 2 tumours where the treatment was known, it was watchful waiting in 15 (62.5%), radio-therapy in 5 (20.8%) and radical prostatectomy in 4 (16.7%).

Analysis of the data according to race showed that in the group of 47 black men there was a higher percentage of clinically abnormal DRE, PSA > 4.0 ng/ml and biopsies showing malignancy and a higher overall prostate cancer detection rate, whereas the mean and median IPSS was lower than in the other race groups (Table III).

DISCUSSION

Although serum PSA is the most powerful tool for the detection of early stage prostate cancer, it is not specific for prostate cancer. Elevated PSA levels can be caused by BPH, prostatitis, prostatic infarction, prostatic intra-epithelial neoplasia (PIN) and perturbations of the prostate such as biopsy or transurethral resection (TURP).[22] Furthermore, not all prostate cancers give rise to an elevated PSA.[23]

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Table I. Findings with regard to DRE, serum PSA and TRUS-guided prostate biopsy

	N	% of 1 056 men	% of subgroup
DRE clinically benign	964	91.3	
DRE clinically malignant	32	3.0	
DRE clinically suspicious	49	4.6	
DRE not done or recorded	11	1.0	
DRE abnormal (malignant + suspicious)	81	7.7	
PSA > 4.0 ng/ml	102	9.7	
DRE abnormal plus PSA > 4.0 ng/ml	35	3.3	
DRE abnormal and/or PSA > 4.0 ng/ml	160	15.2	
Preferred referral to private urologist	41		25.6 (N = 160)
Prostate biopsies obtained	114		71.3 (N = 160)
Prostate cancer on first biopsy	37	3.5	32.5 (N = 114)

Table II. Prostate biopsy results in subgroups of men

	DRE abnormal	PSA > 4.0 ng/ml	DRE abnormal + PSA > 4.0 ng/ml
Number in subgroup	81	102	35
DRE clinically abnormal (%)		24 (23.9)	
Serum PSA > 4.0 ng/ml (%)	22 (27.2)		
Prostate biopsy performed (%)	53 (65.4)	75 (73.5)	31 (88.6)
Prostate cancer detected (% of subgroup)	19 (35.9)	31 (41.3)	18 (58.1)
Prostate cancer detected (% of entire cohort of 1 056)	19 (1.8)	31 (2.9)	18 (1.7)

Table III. Comparison of findings in different race groups

	White	Coloured	Black	Asian
DRE abnormal (%)	8.2	6.6	12.8	2.6
PSA > 4.0 ng/ml (%)	9.3	7.7	21.3	15
Biopsies showing prostate cancer (%)	34.3	27.3	50	25
Incidence of cancer (%)	3.7	2.7	8.5	2.5
IPSS mean	9.6	10.8	7.2	12.0
IPSS median	7	8	6	10.5

The use of PSA and DRE will detect prostate cancer in approximately 4% of subjects in a population-based screening programme, but in a clinic population of symptomatic urological patients detection rates up to 14.6% have been described, showing that the detection rate is strongly population dependent.[24] Overall, in most screening studies approximately 5 biopsies are needed to detect 1 carcinoma.[25] In our study approximately 3 biopsies were required to diagnose 1 prostate cancer.

In a study of 31 953 eligible subjects screened in centres throughout the USA, the prostate cancer detection rate for PSA was 3.6%, for DRE 3.0%, and if both tests were positive it was 4.7%.[14] The positive predictive value for an elevated PSA level was 31.6%, whereas for DRE it was 25.5%. Overall, 31% of

cancers were missed by DRE and diagnosed by PSA only, while DRE detected 27.6% of cancers that would have been missed by PSA.[14]

In the European Randomised Study of Screening for Prostate Cancer (ERSPC),[26] 10 865 men underwent a serum PSA determination and in 1 368 cases (12.6%) the PSA level was greater than 3.9 ng/ml.[26] Biopsies were performed in 1 239 (90.6%) of these men and detected prostate cancer in 373 (30.2%), i.e. in 3.4% overall. In 2 619 men a biopsy was indicated by either abnormal DRE and/or TRUS findings or a serum PSA > 3.9 ng/ml. Biopsies were performed in 2 365 cases (90.3%), and cancer was detected in 505 (21.4%) men for an overall cancer detection rate of 4.7%.[26]

In our study the overall prostate cancer detection rate was 3.5%. The fact that this is somewhat lower than the 4.7% found in larger studies may be due to the fact that prostate biopsies were obtained in only 71% of our cases where they were indicated, which is lower than the 90% biopsy rate in the ERSPC study.[26] Prostate cancer was found on the first biopsy in 32.5% of our patients, which is somewhat higher than the 21.4% in the ERSPC study.[26] This may be due to somewhat stricter selection criteria for prostate biopsy in our study, e.g. a PSA cut-off of 4.0 ng/ml instead of 3.9 ng/ml.

In our study the lowest biopsy rate (65.4%) was in patients who had only an abnormal DRE, whereas the highest biopsy rate (88.6%) was in men with both an abnormal DRE and an elevated PSA. This probably indicates reluctance on the part of the physician to refer the patient for prostate biopsy solely on the basis of an abnormal DRE. There is considerable inter-examiner variability in DRE, indicating that experience plays an important role in evaluation of the prostate by means of DRE. Nonetheless, DRE significantly increases the detection rate that can be achieved with PSA alone.[17]

In our study the positive predictive value (PPV) of an elevated PSA for the presence of cancer on prostate biopsy (41.3%) is higher than the 31.6% and 30.2% found in other studies.[14,26] In our study the PPV of an abnormal DRE was 35.9%, compared with 25.5% in a study from the USA.[14] This may be due to a greater reluctance in our study to obtain a biopsy unless the PSA was significantly elevated or the DRE was clearly abnormal. Our PPV for the combination of an abnormal DRE plus elevated PSA was 58.1%, which confirms the usefulness of combining DRE with PSA measurement, even though in some European screening studies the use of DRE has now been abandoned in favour of a lower PSA cut-off level of 3.2 ng/ml.[4]

The question of re-screening men with an initially normal PSA is still controversial. Re-screening at 6-monthly or yearly intervals leads to a significant decrease in the prostate cancer detection frequency (from 3% to less than 1%), and a 2-year screening interval has been suggested for men with PSA levels lower than 2 ng/ml.[27,28] In patients with an indication for prostate biopsy where no malignancy is found, a second sextant biopsy within 6 months may reveal up to 23% additional cases of prostate cancer.[29] Therefore, in our study follow-up of men with a negative first prostatic biopsy will undoubtedly reveal more cases of cancer.

The racial distribution among men attending our prostate clinic was white 59.5%, coloured plus Asian 36.1%, and black 4.5%. When compared with the racial distribution of men seen at our oncology clinic (coloured plus Asian 51%, white 44% and black 4%), the proportion of white patients attending the prostate clinic was higher. This probably reflects greater awareness of prostate cancer and more favourable socio-economic conditions in this population group (e.g. access to a

telephone, transport, ability to take time off from work to attend the prostate clinic).

In our study black men had a higher percentage of clinically abnormal DRE, PSA > 4.0 ng/ml and biopsies showing malignancy and a higher overall detection rate of prostate cancer (Table III). The fact that the mean and median IPSSs were lower in black patients than in the other race groups seems to indicate that the higher detection rate of prostate cancer was not due to the fact that these men sought counselling because they were more symptomatic. However, the lower IPSS score may also be due to a higher symptom threshold, or to differences in the interpretation of the IPSS questionnaire. Furthermore, these data have to be interpreted with caution, since black men comprised only 4.5% of our overall study cohort.

A major part of serum PSA occurs as a complex between PSA and α1-antichymotrypsin (ACT). Patients with prostate cancer have a significantly higher proportion of complexed PSA (PSA-ACT) than those with BPH. Therefore, men with a relatively low free/total PSA ratio are more likely to have cancer.[30] The free/total PSA ratio may be used to decrease the number of biopsies in patients with an intermediate PSA of 4.0 - 10.0 ng/ml.[25] Various cut-off levels for the free/total ratio have been suggested, varying between 0.15 and 0.21, but cut-off values for clinical practice have not yet been established.[31] In our study there was a statistically significant difference in the free/total PSA ratio between those with and without prostate cancer on biopsy. However, there was considerable overlap in the range of free/total PSA values between the two groups. Nonetheless, if there is doubt about the necessity for a prostate biopsy (e.g. PSA marginally elevated, DRE suspicious but not clearly abnormal), a free/total PSA ratio < 0.15 may be a strong indicator that biopsy is indeed required.

The clinical stage distribution in 459 cases of prostate cancer diagnosed in the Rotterdam section of the ERSPC study was T1 in 25%, T2 in 52%, T3 in 20%, T4 in 1% and metastatic to lymph nodes or bone (N1 or M1) in 2%.[4] Therefore, the cancer was clinically localised in 77% of the patients in the ERSPC study, which is comparable to the 83.8% of clinically localised tumours found in our study.

However, a worrying aspect of our study is that in the men diagnosed with clinically localised prostate cancer, the treatment chosen was watchful waiting in 62.5% of cases, radiotherapy in 20.8% and radical prostatectomy in 16.7%; potentially curative treatment was therefore given in only 37.5% of cases. This is not much different from the historical cohort of symptomatic men seen from 1976 to 1996 at our oncology clinic, where patients with potentially curable early stage disease were treated with radiotherapy in 42% of cases, watchful waiting in 39%, radical prostatectomy in 11% and hormonal treatment in 8%, i.e. 53% received potentially curative treatment.[9] In comparison, in the ERSPC study 38% of

patients chose radical prostatectomy, 51% received radiotherapy, watchful waiting was chosen by 8% and 2% received endocrine therapy, i.e. potentially curative treatment was given in 89% of cases.[4]

Many questions about the optimal treatment of early stage prostate cancer remain controversial. Both radical prostatectomy and radiotherapy (external beam or brachytherapy) can cure the majority of patients with early stage prostate cancer, but it is not clear which is the better treatment, since no prospective, randomised comparisons have been done. Recently, large randomised trials have been initiated to compare radical prostatectomy and watchful waiting in the management of early stage prostate cancer, but their results will not be available for at least another decade.[32,33] However, with regard to quality-of-life issues, radical prostatectomy is well accepted by at least 89% of patients who have undergone this procedure, whereas watchful waiting has been shown to increase anxiety among patients.[34]

CONCLUSIONS

Of 1 056 men who attended our prostate clinic for early detection of prostate cancer, the majority were relatively asymptomatic. Prostate cancer was found on the first biopsy in 3.5% of cases (with a possible higher incidence among black men), and 84% of the men had potentially curable (early stage) prostate cancer. However, in these men potentially curative treatment was given in only 37.5% of cases, which compares unfavourably with screening studies done in Europe and with our own treatment of symptomatic patients seen over the last 20 years at Tygerberg Hospital, where curative treatment was offered in 89% and 53% of cases, respectively.

References

1. Sitas F. Histologically diagnosed cancers in South Africa. S Afr Med J 1994; 84: 344.
2. Montie JE, Pienta KJ. A unifying model to explain the increased incidence and higher mortality of prostate cancer in black men. Urology 1999; 53: 1073-1076.
3. Glover FE jun., Coffey DS, Douglas LL, et al. The epidemiology of prostate cancer in Jamaica. J Urol 1998; 159: 1984-1987.
4. Rietbergen JBW, Hoedemaeker RF, Kruger AE, Kirkels WJ, Schröder FH. The changing pattern of prostate cancer at the time of diagnosis: characteristics of screen detected prostate cancer in a population based screening study. J Urol 1999; 161: 1192-1198.
5. Albertsen PC, Fryback DG, Storer BE, Kolon TF, Fine J. Long-term survival among men with conservatively treated localized prostate cancer. JAMA 1995; 274: 626-631.
6. Potosky AL, Miller BA, Albertsen PC, Kramer BS. The role of increasing detection in the rising incidence of prostate cancer. JAMA 1995; 273: 548-552.
7. Stephenson RA, Smart CR, Mineau GR, James BC, Janerich DT, Dibble RL. The fall in incidence of prostate carcinoma. Cancer 1996; 77: 1342-1348.
8. Hoeksema MJ, Law C. Cancer mortality rates fall: a turning point for the nation. J Natl Cancer Inst 1996; 88: 1706-1707.
9. Stopforth HB, Heyns CF, Allen FJ. Profile of prostate cancer in the Western Cape Province, South Africa. African Journal of Urology 1998; 4: 56-60.
10. Murphy GP, Natarajan N, Pontes JE, et al. The national survey of prostate cancer in the United States by the American College of Surgeons. J Urol 1982; 127: 928-934.
11. Visser O, Horenblas S. Incidentie en behandeling van prostaatcarcinoom in de regio van het integraal kankercentrum Amsterdam, 1989-1994. Ned Tijdschr Geneeskd 1996; 140: 2627-2631.
12. Catalona WJ, Hudson MA, Scardino PT, et al. Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: receiver operating characteristic curves. J Urol 1994; 152: 2037-2042.
13. Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. N Engl J Med 1991; 324: 1156-1161.
14. Crawford ED, DeAntoni EP, Etzioni R, Schaefer VC, Olson RM, Ross CA. Serum prostate-specific antigen and digital rectal examination for early detection of prostate cancer in a national community based program. The Prostate Cancer Education Council. Urology 1996; 47: 863-869.
15. Rietbergen JBW, Kranse R, Kirkels WJ, de Koning HJ, Schröder FH. Evaluation of PSA, DRE and TRUS in population based screening for prostate cancer: suggestions to improve the efficacy of early detection. Br J Urol 1997; 79: suppl 2, 57-63.
16. Labrie F, Dupont A, Suburu R, et al. Serum prostate specific antigen as pre-screening test for prostate cancer. J Urol 1992; 147: Part 2, 846-851.
17. Smith DS, Catalona WJ. Interexaminer variability of digital rectal examination in detecting prostate cancer. Urology 1995; 45(1): 70-74.
18. Terris MK, McNeal JE, Stamey TA. Detection of clinically significant prostate cancer by transrectal ultrasound guided systematic biopsies. J Urol 1992; 148: 829-832.
19. Daneshgari F, Taylor GD, Miller GJ, Crawford ED. Computer simulation of the probability of detecting low volume carcinoma of the prostate with six random systematic core biopsies. Urology 1995; 45: 604-609.
20. Rietbergen JBW, Boeken Kruger AE, Kranse R, Schröder FH. Complications of transrectal ultrasound guided systematic sextant biopsies of the prostate: evaluation of complication rates and risk factors within a population based screening program. Urology 1997; 49: 875-880.
21. King C, Friese J, Lauren L, et al. Measurement on IMX of free and total forms of prostate specific antigen for differentiation of patients with benign prostatic hyperplasia and prostate cancer. Clin Chem 1994; 40: 1007-1010.
22. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumormarker for adenocarcinoma of the prostate. J Urol 1991; 145: 907-923.
23. Spencer JA, Alexander AA, Gomella L, Matteucci T, Goldberg BB. Clinical and ultrasound findings in prostate cancer: patients with normal prostate specific antigen levels. Radiology 1993; 189: 389-393.
24. Cooner WH, Mosley BR, Rutherford CL jun., et al. Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. J Urol 1990; 143: 1146-1152.
25. Bangma CHH, Rietbergen JBW, Kranse R, Blijenberg BG, Petterson K, Schröder FH. The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population. J Urol 1997; 157: 2191-2196.
26. Rietbergen JBW, Kranse R, Hoedemaeker RF, et al. Comparison of PSA corrected for total prostate volume and transition zone volume in a population based screening study. Urology 1998; 52: 237-246.
27. Smith DS, Catalona WJ, Herschman JD. Longitudinal screening for prostate cancer with prostate specific antigen. JAMA 1996; 276: 1309-1315.
28. Carter HB, Epstein JI, Chan DW, Fozard JL, Pearson JD. Recommended prostate specific antigen testing intervals for the detection of curable prostate cancer. JAMA 1997; 277: 1456-1460.
29. Roehrborn CG, Pickens GJ, Sander JS. Diagnostic yield of repeated transrectal ultrasound-guided biopsies stratified by specific histopathologic diagnoses and prostate specific antigen levels. Urology 1996; 47: 347-352.
30. Stenman UH, Leinonen J, Alfthan H, Rannikko S, Tuhkanen K, Alfthan O. A complex between prostate specific antigen and α1-antichymotrypsin is the major form of prostate specific antigen in serum of patients with prostatic cancer. Assay of the complex improves clinical sensitivity for cancer. Cancer Res 1991; 51(1): 222-226.
31. Roehrborn CG, Gregory A, McConnell JD, Sagalowsky AI, Wians FH jun. Comparison of three assays for total serum prostate-specific antigen and percentages of free prostate-specific antigen in predicting prostate histology. Urology 1996; 48: suppl, 23-32.
32. Wilt TJ, Brawer MK. The Prostate Cancer Intervention Versus Observation Trial: a randomized trial comparing radical prostatectomy versus expectant management for the treatment of clinically localized prostate cancer. J Urol 1994; 152: Part 2, 1910-1914.
33. Norlen BJ. Swedish randomized trial of radical prostatectomy versus watchful waiting. Canadian Journal of Oncology 1994; 4: suppl, 38-40.
34. Fowler FJ jun., Barry MJ, Lu-Yao G, Wasson J, Roman A, Wennberg J. Effect of radical prostatectomy for prostate cancer on patient quality of life: results from a Medicare survey. Urology 1995; 45: 1007-1013.