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Acknowledgements—This work was partially supported by AIRC and CNR project n. 11.

Eur J Cancer, Vol. 29A, No. 6, pp. 804–811, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00
Pergamon Press Ltd

Modalities Available for Screening for Prostate Cancer

Frans M. Bentvelsen and Fritz H. Schröder

INTRODUCTION

IN THE EUROPEAN COMMUNITY (E.C.) carcinoma of the prostate is the second leading cause of cancer deaths among men after carcinoma of the lung [1]. The death rate was 22.6 per 100 000 men during the years of 1980–1984 (9% of all male deaths of cancer). Within the E.C. 85 000 new cases are diagnosed per year. In the U.S.A. prostate cancer has become the most commonly diagnosed cancer in males. In 1992, 132 000 new cases are expected. Over a 13-year period from 1973 to 1985 the age-adjusted incidence of prostate cancer has increased at a rate of 2.2% per year in the U.S.A. The age-adjusted mortality increased 0.8% annually [2]. In the Germany, France, Belgium and the Netherlands the age-adjusted mortality is similar to that of the U.S.A. In comparison with the U.S.A., the number of deaths due to prostate cancer in the Netherlands has increased by 2% annually over the past 10 years [3]. One explanation for this increase lies in the fact that men now live longer, to an age at which prostate cancer becomes sufficiently advanced to cause death. Moreover, the reporting of the disease may be increased [4]. The increase of prostate cancer deaths is poorly understood. Possibly, after correction for these factors the mortality would not appear to increase at all.

Unfortunately, at the time of initial presentation most patients exhibit evidence of advanced disease. Curative treatment of prostate cancer is only possible if the disease is detected before metastases are present and the cancer is still confined to the prostate gland.

The high mortality on one hand and the availability of apparently effective treatment of locally confined disease by surgery on the other warrants reconsideration of early detection studies. For this reason the availability of accurate screening tests is a prerequisite. Digital rectal examination (DRE), prostate-specific antigen (PSA) and transrectal ultrasonography (TRUS) are available. The question is: are these tests suited for early detection studies and screening programs?

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Revised 17 July 1992; accepted 27 Nov. 1992.

DEFINITIONS

When discussing screening studies it is important to understand statistical terms often used [5]. The term 'sensitivity' of a test refers to the number of patients who actually have the disease and in whom the test is positive, divided by the total number of patients with the disease. The term 'specificity' refers to the number of men who actually do not have the disease and in whom the test is negative, divided by the total number of men without the disease. The term 'positive predictive value' (PPV) is the probability that the disease is, in fact, present given a positive test result.

The PPV is strongly influenced by the prevalence of the disease. Patients who come for evaluation in a urological practice probably are not representative of a general population. Therefore, a description of the group of males which was subject to screening or early detection is needed for a sensible comparison of different studies.

The detection rate is the proportion of those who are detected as having the disease within the total screened population.

DIGITAL RECTAL EXAMINATION

DRE is the classic technique for the detection of prostate cancer. The prostatic structures such as apex, basis, median and lateral sulci and the seminal vesicles can be readily palpated transrectally. Rough estimates of the size of the prostate and of lesions within the prostate can be made in a bidimensional fashion. Prostate cancer, if it is confined, will appear as a discrete induration or a nodule (T2). More extensive prostate cancer appears diffusely firm and extends beyond the lateral sulci or into the seminal vesicles (T3). Fixation at the pelvic wall will usually occur at the level of the levator ani muscles (T4). Incidental prostatic cancer (T1) is found in 8–12% of cases when tissue removed for the treatment of benign prostatic hyperplasia (BPH) is examined histologically [6].

If a prostate is suspicious for prostate cancer a biopsy must be taken. Prostatic cancer is confirmed in 22–39% of such cases (Table 1). The differential diagnosis includes BPH, prostatitis, granulomatous prostatitis, prostatic calculi and tuberculosis.

In the 1950s DRE was used by Jensen *et al.* [7] in a screening program involving 4367 asymptomatic men. Over a 10-year period, 36 men were found to have carcinoma of the prostate,

Table 1. Results of prostate cancer screening by digital rectal examination

Source	Detection rate Numbers	%	Positive predictive value Numbers	%	Localised carcinomas Numbers	%
Jensen *et al.* [7]	36/4367	0.82	—		—	
Gilbertsen *et al.* [8]	20/5856	0.34	—		—	
Faul [9]	1951/1.5 × 10^6	0.13	—		—	
Thompson *et al.* [13]	17/2005	0.85	17/65	26	15/17	88
Vihko *et al.* [11]	6/771	0.78	6/27	22	4/6	67
Waaler *et al.* [12]	1/480	0.21	1/16	6	—	
Mueller *et al.* [14]	80/4843	1.7	122/312†	39	46/80	57
Lee *et al.* [17]*	10/784	1.3	10/29	34	16/22†	73
Chodak *et al.* [10]*	31/213	1.5	36/144	25	25/36	69
Pedersen *et al.* [15]	13/1163	1.1	13/45	29	11/13	92
Mettlin *et al.* [26]	33/2425	1.4	33/118	28	20/24	83
Median value		0.85		28		73

*Clinical study.
†Total number reported.

amounting to a detection rate of 0.82%. The authors found that malignancies identified after previously normal DRE were likely to be less advanced in comparison to the initial year of screening.

Using annual DRE between 1948 and 1964 Gilbertsen *et al.* [8] found 75 cases of prostatic carcinoma in 5856 men. Twenty of them were detected on the first examination. The detection rate on the first DRE was thus 0.34%.

In a screening program involving a large population in Germany [9] 1.5 million men were examined. Of the preventive checkups about 80% were performed by general practitioners and internists and only 15% by urologists. The detection rate was 0.13%. Several of the false-negative diagnoses were thought to be due to the lack of experience among general practitioners and internists in conducting DRE.

Chodak *et al.* [10] reported in a self-referred population of 2131 men a detection rate of 1.45% on the initial DRE. The PPV of DRE is calculated to be 25%.

Vihko *et al.* [11] detected 0.78% prostate cancers in 771 volunteer veterans in Finland from World War II.

A surprisingly low detection rate of 0.21% was found by Waaler *et al.* [12] in Norway. Of 480 men aged 45–67 years, 16 men with suspicious findings under DRE underwent biopsy. Only 1 patient was found to have a neoplasm of the prostate.

Thompson *et al.* [13] obtained a detection rate of 0.85% as a result of routine DRE in 2005 men during urological visits. Cancer was histologically confirmed in 26% of the men with an abnormal DRE.

Mueller *et al.* [14] detected 1.65% carcinoma in a clinical group of 4843 men. The subjects underwent 11523 rectal examinations in total during a period of 6 years and 80 tumours were detected on the initial DRE. The overall PPV of rectal examination was calculated to be 39%.

Pedersen *et al.* [15] found a detection rate of 1.12% in a randomly selected population of 1163 men reacting to an invitation. The PPV of a suspect DRE was 30%.

In summary of these clinical early detection studies and screening programs, the PPV of an abnormal DRE ranged from 22 to 39% except for the study of Waaler *et al.* [12] in which the detection rate was exceptionally low.

Detection rate and prevalence

The detection rate ranged from 0.13 to 1.65%. These low values are one reason that DRE alone is not satisfactory for screening for prostate cancer. From pathological studies it is known that many tumours are localised bilaterally or are multifocal, which leads to difficulties in the detection of malignancy of the prostate by DRE. In routine histological examinations of prostates removed by surgery in 8–12% of the specimens an unexpected carcinoma is found. These tumours were not palpable on rectal examination before resection of the prostate.

The true prevalence is higher than the reported highest detection rate of 1.65%. As we know the prevalence in the general male population increases with age. Based on autopsy studies even 30% of men over the age of 50 and about 90% of men aged 90 will have carcinomas on microscopical histological examination of the prostate gland [16]. It is important in screening to find only those cancers which surface clinically and become life threatening. DRE is a poor first-line screening method because of its low sensitivity. In spite of not being very sensitive, DRE may have the specific property to select for clinically important tumours. The use of DRE may protect against over-diagnosis of clinically insignificant, focal lesions. Unfortunately, it also excludes the discovery of some aggressive small or multifocal tumours.

TRANSRECTAL ULTRASONOGRAPHY

TRUS utilises advanced ultrasound technology to visualise the prostate. 5–7.5 MHz transducers are used. To achieve complete visualisation transverse and longitudinal imaging is necessary. This can be achieved by turning a so-called "end firing" transducer by 90° or by using the more recent biplanar probes which allow switching of a sector scanner between the transverse and longitudinal directions (Fig. 1).

With the use of TRUS, the fibrous capsule, the seminal vesicles, the bladder wall, the peripheral zone, the transition zone and the preprostatic sphincter complex can be visualised. Volume determinations of the prostate and structures within the prostate can be carried out with acceptable accuracy.

Prostatic carcinoma appears on TRUS as a hypoechogenic

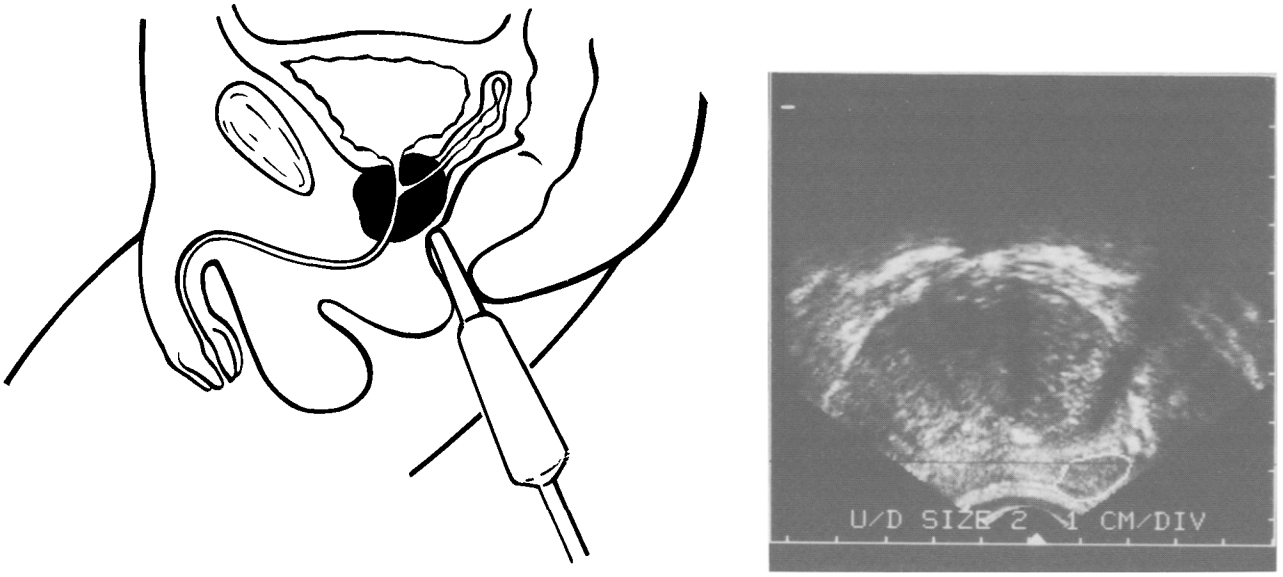

Fig. 1. Schematic diagram of a transrectal ultrasonography of the prostate. Biplanar (end-fire) probe, which allows switching of a sector scanning between the longitudinal and transverse directions. (b) Transverse view of the prostate by transrectal ultrasonography. A hypoechoic area (encircled) represents a localised carcinoma.

(black) lesion in 80% of cases or maybe even more frequently. Figure 1b gives an example. Prostate cancer may also be iso- or hyperechogenic. If TRUS is used for screening the search is exclusively for hypoechogenic lesions. It is uncertain at this time how many carcinomas are missed in this way. The smallest detectable carcinomas have a diameter of 0.7 cm.

TRUS is increasingly used for directing prostatic biopsies. TRUS combined with TRUS directed biopsy detected cancer of the prostate in a study be Lee *et al.* [17] in 2.6% of 784 self-referred men. DRE performed in the same population yielded a detection rate of 1.3%. Because only two of 22 tumours were not noticed by TRUS (12 of the 22 tumours were not found by DRE), the sensitivity for TRUS was defined as two times as high as for DRE (Table 2). The PPV of DRE and TRUS were, respectively, 34 and 31%. When TRUS and DRE were both suspect the PPV increased to 50%.

To the contrary, Vallancien *et al.* [18] detected more cancers by DRE than by TRUS. 167 patients visiting a urological department underwent DRE and TRUS and biopsy of the prostate. DRE established the correct diagnosis in 32 of 39 men having malignancy, TRUS in 27. Based on this result the sensitivity for DRE was 82%, and for TRUS 69%. The PPV for TRUS was 56% at a detection rate of 16.2%.

Table 2. Results of prostate cancer screening by transrectal ultrasonography

Source	Detection rate Numbers	%	Positive predictive value Numbers	%
Lee *et al.* [17]* (self referrals)	20/784	2/6	20/64	31
Watanabe *et al.* [20]	42/6529	0.6	—	—
Rifkin and Choi [21]*	17/329	5.2	17/80	10
Vallancien *et al.* [18]*	27/167	16.2	27/48	21
Ragde *et al.* [22]*	50/1051	4.8	50/138	56
Lee *et al.* [23]* (referred by other physicians)	104/?	—	104/256	36
Cooner *et al.* [24]*	263/1807	14.6	263/835	31.5
Mettlin *et al.* [26]	44/2425	1.8	44/290	15.2
Median value				31

*Clinical study.

Watanabe *et al.* [19] used TRUS for mass screening in 6529 Japanese men and identified prostate cancer in 0.6%. About 10 biopsies were needed to find one cancer [20]. Although in Japan the age-adjusted mortality rate is only less than one fifth of that in Western countries there is no study reported from Europe or from the U.S.A. which investigates ultrasonography as a stand-alone screening tool.

Rifkin and Choi [21] performed TRUS in 329 men: prostate cancer was detected in 17 men, amounting to a detection rate of 5%. A suspicious sonography predicted cancer in 21%.

Ragde *et al.* [22] examined 1051 men responding to an advertisement. Biopsy was performed in 138 men based on sonographic abnormalities. The PPV of such an abnormality turned out to be 36%.

In a population referred by other physicians Lee *et al.* [23] found a PPV of 41% for TRUS. Only 2 patients out of 44 men (5%) had carcinoma confirmed on biopsy and an abnormal TRUS in combination with a normal PSA serum concentration and a normal DRE.

Using a 7 MHz transducer, Cooner *et al.* [24] performed TRUS in 1807 men referred to a urological practice. In those with a suspicious sonogram, biopsy was performed. In 835 biopsied patients the high detection rate of 14.6% was established with a positive predictive value of 31.5%. The predictive value for the combination of an abnormal TRUS with positive DRE was 43.2% in this population. For the combination of an abnormal TRUS and PSA (levels greater than 4 ng/ml using a monoclonal assay) it was 48.4%.

An abnormal PSA predicted cancer in 35%, if PSA and DRE were both abnormal in 60.1%. The positive predictive value of DRE alone was 35.9%. The sensitivity for DRE was 77.2%, the specificity 76.5%.

When PSA was > 10 ng/ml and DRE was normal, cancer of

the prostate was present in 28%. Based on these data, Stamey [24] argues that a normal DRE when combined with a PSA level greater than 10, is cost effective to justify a biopsy.

Screening with TRUS

Cooner's series included 1305 men aged 55–75 years, and in only 123 of 374 abnormal rectal examinations was prostate cancer detected. In total, 170 cancers were found. Of the 47 men with malignancy missed by DRE, 31 had abnormal, and 16 had normal PSA. PSA contributed 2.4% and TRUS added 1.2% to an overall detection rate of 13% in this age-selected subgroup.

Cooner stated that if sonographic criteria are used for biopsy, identification of small lesions would be prevented. TRUS would avoid small microscopic cancers of which clinical significance is not established. Only the more advanced cancers would be discovered by TRUS. This statement regarding tumour volume and TRUS is contrary to the experience of Palken *et al.* [25]: the tumour volume of 30 radical prostatectomy specimens was compared to preoperative TRUS, DRE and PSA. TRUS was a poor predictor of tumour volume. PSA level alone correlated with tumour volume.

Preliminary results of the American Cancer Society National Cancer Detection Project [26] displayed an overall detection rate of 2.4% in 2425 healthy volunteers 55–70 years of age. DRE discovered cancer of the prostate in 33 and TRUS in 44 of the 2425 initial examinations. Based on 57 cancers found in this population, the reported sensitivity for TRUS and DRE was, respectively, 77.2 and 57.9%. The greater sensitivity for TRUS was achieved at the expense of a lower specificity for TRUS.

The positive predictive value of TRUS was 15.2%. Cancer was present in 28% of men with a suspicious DRE. When biopsy was recommended by both tests cancer was found in 32%. An elevated PSA level alone did not indicate a recommendation for biopsy in this study. However, in 92% of the participants the PSA was determined. In cases of cancers that were found by an abnormal DRE or TRUS, in 58% of these patients PSA was also elevated (PSA more than 4.0 ng/ml using a monoclonal assay or more than 7.0 ng/ml using a polyclonal assay).

When TRUS and DRE were in agreement in recommending biopsy, the PPV in men with a normal serum PSA level and with an elevated PSA level was, respectively, 14.6 and 68%. In these clinical studies which compared TRUS to DRE a sensitivity ranging from 45 to 82% is calculated. The sensitivity of TRUS in the detection of prostate cancer ranges from 60 to 91% [27].

Calculating sensitivity (and specificity) for screening implies that the presence of prostate cancer is known in the population under study. In fact, no other gold standard for prevalence of prostate cancer exists, other than histological examination of the whole prostate.

In an autopsy study TRUS was done on 63 patients [28]: with a premortem DRE without suspicion 19 prostatic tumours were found at autopsy. The capacity of TRUS to detect prostatic tumour was correlated to the cancers in the prostate specimens; the sensitivity (32%) and the specificity (64%) of TRUS appeared too low for use in screening, if added to a normal DRE. Furthermore, because DRE is inexpensive and easier to perform than TRUS, there appears to be only little gain of a higher sensitivity by screening with TRUS as the primary test.

The PPV of TRUS ranges from 15.2 to 56%, excluding the Japanese study [20]. However, it must be remembered that differences in prevalance between a referral population and an asymptomatic group are difficult to estimate. For example, only one of seven biopsies recommended by TRUS revealed cancer in the screening study of Mettlin *et al.* [26] in contrast to the clinical studies.

PROSTATE SPECIFIC ANTIGEN

The identification of PSA [29] has increased the methods available for early detection of prostate cancer. Ideally, a screening test should be performed on easily obtainable body fluids such as urine or blood. The test should not only identify patients with the disease, but should allow differentiation of those individuals whose disease is potentially progressive from those having more dormant tumours, which will not progress. Advantages of PSA are that PSA is determined in plasma, and the marker is objective and measured in a quantitative way. Sensitivity and specificity can be tuned by changing the operational upper limit of normal. This tool of screening in contrary to DRE and TRUS is independent of the examiners skill.

At our institution the sensitivity and specificity of PSA as an indicator of prostatic cancer was studied in a retrospective fashion in 476 men in comparison to prostatic acid phosphatase (PAP) [30, 31]. PSA was determined in normal elderly men and patients with BPH and with carcinoma of the prostate. The study was carried out by using the Hybritech Tandem-R monoclonal immunometric assay.

Normal value

In the literature different values have been indicated as the upper limit of normal: Chan recommended 2.8 [32], many other authors suggested 4.0 [33, 34], Sidall [35] used an operational limit of 10 ng/ml.

Our material was used to find a cutoff level, because of the ongoing discussion about normal values. For the control group, blood samples were obtained from 127 hospitalised males without urological complaints. DRE was done to rule out BPH or cancer. In the control group a normal value of 5.0 ng/ml was found for PSA and 2.2 ng/ml for PAP.

Specificity

Blood samples were also obtained from 187 patients with BPH before resection of the prostate (malignancy in the resected tissue was excluded histologically routinely). However, comparing these observations to similar observations in the control group, a cutoff value of 10 instead of 5 ng/ml has to be used. At the normal value of 5.0 for PSA in the BPH group the specificity (in excluding prostatic cancer) was only 59%, while it was 79% for PAP at the cutoff value of 2.2 ng/ml. Due to this substantial false-positive rate, instead of 5 ng/ml a cutoff value of 10 ng/ml was used. 20% of patients with BPH had levels above 10 ng/ml. PSA remained (at a relatively high cutoff value) a more sensitive marker for prostatic cancer than PAP. The change of the normal value improved the specificity from 59 to 80% in the BPH group.

It was concluded that because of a specificity of 80% in men with BPH, PSA cannot be considered a specific parameter for screening cancer. However, this conclusion was based on two wrong assumptions:

(1) A specificity of 80% for the PSA test with a cutoff level of 10 ng/ml was found in symptomatic BPH patients before surgery; the specificity in asymptomatic men in a random screening population may be much higher. Symptoms caused by inflammation of the prostate [36] are associated with an elevation in serum PSA. The clinically determined specificity cannot be applied to an asymptomatic population of men.
(2) Patients with symptomatic BPH have larger prostates on the

Table 3. PSA values (ng/ml) in benign prostatic hyperplasia in clinical studies*

Source	PSA > 4 Numbers	%	PSA > 10 Numbers	%
Ercole *et al.* [38] 1987	75/375	21	10/357	3
Ferro *et al.* [44] 1987	—		13/40	33
Oesterling *et al.* [39] 1988	34/72	47	7/72	10
Cooner *et al.* [40] 1988	40/197	20	8/197	4
v. Dieijen-Visser *et al.* [43] 1988	—		12/96	12
Armitage *et al.* [45] 1988	71/139	59	27/139	22
Hudson *et al.* [41] 1989	35/168	21	3/168	2
Allhof *et al.* [42] 1989	—		73/696	10
Bentvelsen *et al.* [30] 1990	95/187	51	37/187	20
Median value		21		10

*Tandem-R PSA; Hybritech.

average than men with BPH in an asymptomatic population. In autopsy studies the volumes of clinically benign whole prostates have been correlated with premortem PSA levels [37]. A positive correlation between prostatic volume and PSA was measured.

This influenced the clinically found specificity of our study. In only 6% of BPH patients with removed prostate tissue less than 20 g (n = 96), we found PSA levels above 10 ng/ml. In contrast, in 43% with a prostate weight greater than 40 g (n = 37) PSA was above 10 ng/ml. The high number of patients with a very large prostate weight in our study might have contributed to a reduced specificity of 80% in the BPH patients.

In patients with histologically proven BPH (Table 3) Ercole *et al.* [38] found a PSA over 10 ng/ml in only 3%, Oesterling *et al.* [39] discovered a PSA greater than 10 ng/ml in 10%, Cooner *et al.* [40] found an elevated PSA in 4%, Hudson *et al.* [41] in only 2%, Allhof *et al.* [42] in 10%, and van Dieijen-Visser *et al.* [43] in 12%. Ferro *et al.* [44] found, however, an elevated PSA in 33%. This percentage of BPH with elevated serum PSA was much higher than in our study. Some papers mentioned the weight of the removed prostate: Armitage *et al.* [45] described a correlation between the weight of the resected prostatic tissue and the PSA level. In 22% of cases, PSA was elevated above 10 ng/ml. With a polyclonal PSA assay Stamey *et al.* [46] estimated the PSA elevation due to each gram of BPH tissue.

To improve specificity of PSA in evaluation of men with enlarged prostates, the term "PSA index" or "PSA density" has been introduced. Since the volume of the prostate can be measured by TRUS, correction of elevated PSA levels is thought to be possible by applying the quotient of serum PSA level and prostate volume. Benson *et al.* [47] calculated the serum PSA/volume ratio in patients with PSA levels between 4 and 10 ng/ml (in a clinical study). In 533 men 98 had prostate cancer found upon biopsy, while in 191 no cancer was identified by biopsy (244 patients did not undergo biopsy). The mean PSA values were 7.0 and 6.8 ng/ml for the positive biopsy and the negative biopsy groups, respectively. The prostate volumes were 28.9 and 40.1 ml. The mean PSA density values were 0.297 and 0.208, respectively. It was shown that the mean PSA density values between the positive biopsy and the negative biopsy groups were significantly different, while the mean PSA values were not. The authors claimed a significant advantage of the PSA density over PSA determination alone. When it is assumed that the patients who did not undergo biopsy were free of cancer, the probability of having prostate cancer at a PSA density level < 0.150 and normal DRE and TRUS was less than 10%. Cooner recently advised performance of random biopsies in men whose PSA densities are > 0.150 with otherwise a non-suspicious DRE or TRUS and PSA levels between 4 and 10 ng/ml.

However, these data from clinical studies cannot be applied to an asymptomatic screening population (with or without correction for prostate volume). The value of PSA for screening will have to be established in asymptomatic, randomly identified men.

Sensitivity in clinical studies

In clinical patients with prostate cancer, Catalona found in 21% of the cases a PSA < 4 ng/ml [49]. In the series of Cooner *et al.* [24], 80.2% of prostate cancer patients had a PSA of > 4 ng/ml. At a limit of 10 ng/ml the sensitivity was 52.1%. A survey of the sensitivity of PSA at a cutoff level of 10 ng/ml ranges from 34 to 67% in localised prostate cancer (Table 4).

In clinical studies, in autopsy studies and in a murine model for prostate cancer a high degree of correlation is measured between serum PSA increase and tumour volume [25, 37, 46, 48]. Observation of small tumours may avoid over-diagnosis of non-life threatening focal cancers in screening if only those patients with a rising PSA are treated.

Screening with PSA

PSA as a first-line screening tool in an asymptomatic population was used by Catalona *et al.* at a normal value > 4.0 ng/ml [49]. To establish the value of PSA for screening in combination with other tools (DRE and TRUS) a study in volunteers of 50 or more years of age was performed. If the PSA was abnormal (> 4.0 ng/ml), the measurement was repeated and DRE, TRUS and biopsy followed if the value remained abnormal. Of 4293 volunteers 88% had a normal PSA. In 10% PSA was between 4 and 10 ng/ml. In 2% PSA was greater than 10. In 422 men with a serum PSA between 4 and 10 ng/ml, in 304 of these a second PSA measurement resulted in a value greater than 4 again. In 240 participants TRUS-guided biopsy was done. One quarter of these subjects (58 men) had prostate cancer, about 75% of these carcinomas were locally confined. In 78 men the PSA value was > 10 ng/ml: 60% (47 men) had prostatic carcinoma, only one third of the carcinomas were organ-confined. In summary, 105 of the 4293 volunteers had prostate cancer (56% of them had organ-confined tumours). The detection rate was 2.45%. The

Table 4. PSA values (ng/ml) in clinical localised prostate cancer*

Source	PSA > 4 Numbers	%	PSA > 10 Numbers	%
Sidall *et al.* [35] 1986	—		39/91	43
Ercole *et al.* [38] 1987	—		28/74	38
Ferro *et al.* [42] 1987	—		16/24	67
Armitage *et al.* [45] 1988	—		30/88	34
Hudson *et al.* [41] 1989	64/103	62	37/103	36
Bentvelsen *et al.* [30] 1990	68/88	77	50/88	57
Cooner *et al.* [24] 1990	211/263	80	137/263	52
Catalona *et al.* [49] 1991	—	79		
Median value		77		43

*Tandem-R PSA; Hybritech.

PPV of the PSA test was 33% (Table 5). This ongoing screening study showed a detection rate for PSA greater than the figures that have been mentioned in the literature for DRE.

After enlargement of the study to 10212 men, Catalona compared the screening results with those in 274 concurrently studied men over 50 who were biopsied because of a suspicious DRE.

The disease was not only clinically but also pathologically staged, which resulted in upstaging after surgery in 40% of the cases. The incidence of advanced prostatic carcinoma was lower in the patients screened with an initial PSA measurement (41% of 193), or after serial PSA determinations (30% of 46) than in those whose cancer was diagnosed because of an abnormal rectal examination (67% of 36) [50].

Brawer *et al.* [51] measured PSA levels in 1249 men older than 50 years recruited by advertising: 15% had a PSA level > 4.0 ng/ml. The PPV for PSA levels between 4.1 and 10 ng/ml was 26.5%, > 10 ng/ml the PPV was 50%.

Unfortunately, in this study and in the study by Catalona *et al.* [49], no further diagnostic tests were applied if the PSA value was < 4.0 ng/ml. While 886 of the screened men fell into this category it remains unknown how many cancers were missed and whether this cut-off value can be considered "safe". Mettlin *et al.* [26] found that 29/88 men with cancer found in their early detection program in asymptomatic men had PSA values of < 4.0 ng/ml.

Labrie *et al.* [52] did a PSA test, DRE and TRUS in 1002 randomly selected men between 45 and 80 years. A PSA level below 4 ng/ml was found in 88% of the investigated population. The risk of having prostate cancer at a PSA below 4 ng/ml detected by DRE or TRUS was still 1.9%. Therefore, the authors proposed an even lower PSA cut-off level of 3 ng/ml to decrease the percentage of missed cancers to 1.4%.

PSA was between 4 and 10 ng/ml in 9% of the population. Between these PSA levels the PPV of PSA was 26%. In the remaining 3% of men, PSA was above 10 ng/ml. Biopsy-proven prostate cancer was present in 51% in this high-risk group.

CONCLUSION

PSA, DRE and TRUS are useful in deciding whether a biopsy is indicated or not in screening for localised prostate cancer. The older screening studies with DRE as a "stand-alone" screening tool yielded a detection rate (and a presumed sensitivity) too low for mass screening.

Table 5. Summary of prostate cancer screening in asymptomatic men in combination with clinical early detection studies (median values)

Method	Detection rate	Sensitivity	Positive predictive value
Digital rectal examination	0.85% (Table 1)	45–82%	28% (Table 1)
Transrectal ultrasonography	1.8%* (Table 2)	60–91%	31% (Table 2)
PSA > 4 ng/ml	2.45%*	77% (Table 4)	24%*, †
PSA > 10 ng/ml		43% (Table 4)	60%*

*No median value.
†PSA between 4 and 10 ng/ml.

Later, in clinical studies comparing TRUS to DRE, a higher sensitivity for TRUS was established. Another improvement was the technique of guiding the needle during biopsy of the prostate gland by TRUS. However, the PPV of suspicious lesions found by this expensive method was not high enough to be considered efficient enough as an independent screening tool. This analysis provides data that refute the enthusiasm for TRUS as a primary screening tool alone or next to DRE, in particular when DRE is done in combination with a serum PSA test.

PSA is a third method for screening. In clinical populations the specificity may be very low because of many elevated serum levels in patients with BPH. Recently, however, the first reports of screening studies in healthy volunteers, done in the U.S.A. and Canada, suggest that PSA can be used as a screening tool (in a complementary way to DRE). The PPV of PSA even at a cutoff value of 4 ng/ml was sufficient to warrant a biopsy in contrary to what was expected according to the clinical studies. It seems that at least 24% of all asymptomatic men with prostatic cancer have a serum PSA between 4 and 10 ng/ml and more than half the men have a PSA > 10 ng/ml. The risk of finding an incurable prostate cancer is higher, as the level of PSA increases.

Considering its sensitivity, PSA in symptomatic urological patients is not adequate to detect all prostate cancers which exist on the basis of autopsy studies. Some are detected by DRE or TRUS, before PSA is elevated. In screening PSA must be considered as an adjunct to DRE. Although TRUS clearly can image some non-palpable tumours, the procedure is not indicated for screening of prostate cancer if both PSA and DRE are normal.

Since a positive relationship between tumour volume and serum PSA levels has been discovered, it is of great interest to learn how small a tumour must be to be missed by PSA. If small tumours grow they should become detectable in a serial screening program by elevated PSA values in a subsequent screening round [53]. Some authors found that carcinomas identified by DRE at a second evaluation were less advanced in comparison to those found at the initial screening. Based on preliminary results Stamey argues that an annual PSA measurement and an annual DRE are reasonable measures to follow all men older than 50 years [54].

Most of the current American reports advise the use of an algorithm, in which DRE and PSA are the first-line screening tools. If DRE is abnormal a biopsy is advised. If serum PSA is greater than 4 ng/ml TRUS is performed. Every hypoechoic lesion is biopsied. Above a level of 10 ng/ml, if no lesion is seen random biopsies are recommended.

For PSA values between 4 and 10 ng/ml different opinions exist among the investigators. Without a lesion palpable or visualised by TRUS, some recommend random biopsies. Cooner advocates a biopsy only if the PSA density is > 0.150. Others repeat PSA measurements after a period of a few months to half a year and proceed to random biopsies, only when PSA levels are rising. Before screening policies are simply adapted from American studies, the investigation of asymptomatic European populations is clearly indicated because of differences described above. The role of the screening parameters alone or in combination must be defined. In addition, a decrease in cancer mortality must be shown before such policies can be adopted.

In conclusion, for early detection of cancer of the prostate, initial as well as serial screening may result in the diagnosis of less extensive disease at a stage where patients can be cured. However, there are no studies to show yet that screening leads to prolonged survival of prostate cancer. Unless significant data

are available, which show that early detection of prostate cancer leads to an improved cancer mortality in man, mass screening cannot be advocated.

From a cost-efficiency point of view it will be important to identify levels of suspicion at which some tests, preferably TRUS, can be omitted. This is probably possible on the basis of the combination of PSA and DRE or by PSA alone. In spite of a large volume of men being included into studies it is still not possible to answer this question in a rational way. Certainly, the normal value of PSA of 4.0 ng/ml is not a suitable cut-off point to eliminate men from further testing in screening protocols.

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Eur J Cancer, Vol. 29A, No. 6, pp. 811–813, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Papers

Histopathological Grade and Response to Chemotherapy in Advanced Soft Tissue Sarcomas

Søren Daugaard, Martine v. Glabbeke, Torben Schiødt and Henning T. Mouridsen

In a retrospective analysis, we evaluated the possible significance of histopathological grade with regard to response to chemotherapy in advanced soft tissue sarcomas. In three EORTC protocols, the same dose-schedule was used for patients randomised to treatment with doxorubicin as a single agent (75 mg/m^2 every third week). The submitted pathological slides from 94 of these patients were reviewed and graded. The following parameters were subjectively graded (+/++/+++): nuclear pleomorphism, necrosis, cellularity and vascularity. Mitoses were counted in 20 high-power fields, and a final grade assigned as I, II, IIIA or IIIB. The results were tested both with regard to response (complete response + partial response vs. no change + progressive disease) and survival. However, no statistically significant correlations or trends could be demonstrated. Thus, tumour grade, although a prognostic factor by itself, does not seem to be able to predict response to chemotherapy in the advanced stage.
Eur J Cancer, Vol. 29A, No. 6, pp. 811–813, 1993.

INTRODUCTION

LOCALLY RECURRING or metastasising soft tissue sarcomas present a significant therapeutic challenge, especially when surgical and radiotherapeutic treatment options are exhausted. Results with chemotherapy are only moderate; doxorubicin and ifosfamide remain the most effective single agents with average response rates of approximately 20–30% [1, 2]. Ongoing research includes analyses of the dose/response and schedule/response relationships, as well as the testing of new drugs for activity against sarcomas [2].

Sarcomas are heterogenous, morphologically as well as clinically, but so far it has not been possible to identify factors that could predict the probability of response to chemotherapy. One reason is their rarity, which yields inadequate numbers for analysing the importance of individual histological types, even in multi-centre trials. In addition, diagnostic criteria and classifications are changing continuously through the introduction of new entities (e.g. malignant fibrous histiocytoma) and techniques (especially immunohistochemistry). More feasible is correlation of tumour grade to response, but rather few studies have reported their results of such an analysis [3–6].

The EORTC Soft Tissue and Bone Sarcoma Group has used single-agent doxorubicin as a standard for comparison with

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Received 31 Jan. 1992; accepted 3 June 1992.