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Efficient pathway for early detection of prostate cancer concluded from a 5-year prospective study*

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Summary. In a prospective study the statistical characteristics of digital rectal examination (DRE), transrectal ultrasound (TRUS), and serologic determination of prostate-specific antigen (PSA) were assessed in 1230 patients aged over 40 years. The sensitivity, specificity, and positive and negative predictive values were determined to be 80.3%, 69.7%, 58.9%, and 86.7%, respectively, for DRE; 76.5%, 62.3%, 52.3%, and 83.1%, respectively, for TRUS; and 87.9%, 49.6%, 48.5%, and 88.3%, respectively, for PSA (normal level, 4 ng/ml). The data clearly demonstrate the nonsuitability of each single measure for reliable early detection of prostatic carcinoma. Connection of the parameters in all possible combinations under various conditions demonstrated the superiority of the test "DRE and PSA > 4 ng/ml" over DRE as the "gold standard" and all other options. The use of this approach as the first-line raster of an algorithm (outlined herein) would allow the detection of prostatic malignancy with a specificity of 86.5% and a positive predictive value of 74.0%. Supplementing this screen with short-term controls in cases in which only one parameter is positive ("DRE or PSA > 4 ng/ml") might enable the detection of almost all patients with prostate cancer. TRUS did not provide any additional information.

The principle that early diagnosis of most human malignancies enables detection of cancer at a lower and, by definition, more curable stage applies as well for prostate cancer [7]. According to a survey of the American College of Surgeons in 1986 [14], transurethral resection has been the most common means to establish the diagnosis of prostatic neoplasms. Over the last decade, however, the diagnostic approach to prostate cancer has been enriched by the availability of new immunoserologic as well as imaging modalities for routine clinical use. The advances achieved in these fields prompted us in 1987 to evaluate these modalities with respect to their capacity for detecting prostate cancer either alone or in combination and to compare the results with the findings obtained by digital rectal examination (DRE), which at that time was considered the "gold standard".

Patients and methods

In an ongoing prospective study, 1230 men over 40 years of age recruited from the total-patients cohort at our institution were investigated for the potential presence of a prostatic malignancy by clinical, immunochemical, and sonographic means.

Prior to digital rectal examination (DRE), determination of the serum level of prostate-specific antigen (PSA) was performed using initially an immunoradiometric assay and later an immunoenzymatic assay employing monoclonal antibodies (Hybritech, Inc.). According to the recommendation by the manufacturer, the normal reference interval was defined as 0–3.9 ng/ml. DRE and transrectal sonography of the prostate (TRUS) were performed independently by board-certified urologists who had no knowledge of the test results obtained. TRUS was performed in real time using the Combison 320-5 KretzTechnik apparatus equipped with a 7.5-MHz bifocal multiplane transducer as reported previously [1]. Sonographic analysis included irregularities of any kind with respect to the symmetry, size, and contour of the gland and seminal vesicles as well as the margins and the echoic pattern of a detected focus. The echotexture was defined as echopenic, hypoechoic, hyperechoic, or mixed, according to the sonographic phenotype, and was interpreted by the criteria reported before the onset of the study for differentiation between benign and malignant findings, with special respect to hyper- and hypoechoic foci [6, 13]. In equivocal cases of DRE, a transrectal biopsy using a Tru-Cut needle (Travenol) was performed.

Statistical evaluation (by B.S.) included a subgroup of only 376 patients in whom the accuracy of the diagnosis was assured by histology as a comparable reference test, with proven untreated malignancy being determined in 132 cases and proven benign prostatic hyperplasia (BPH), in 244 cases. Staging in cases of prostate cancer was performed according to the TNM classification [8].

In a multiparameter approach, interpretation of differing results poses a problem, since it is unclear which criterion finally has the edge in reaching a conclusive diagnosis. Combination of the results obtained by the modalities employed is possible in either an "and" or an "or"

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connection. For unequivocal judgement of the test combinations chosen in the study, the criteria for selection were defined as follows:

1. The combined test result of two modalities in the "or" connection is considered to be negative if both results are negative with respect to malignant transformation. It is interpreted as being positive if one or both results are positive.
2. The combined test result of two modalities in the "and" connection is considered to be negative if one or both results are negative. It is defined as being positive if both results are positive.
3. The combined test result of three modalities in the "or" connection is considered to be negative if all tests are negative. It is interpreted as being positive if at least one of three tests is positive.
4. The combined test result of three modalities in the "and" connection is considered to be negative if at least one of three tests is negative. It is interpreted as being positive if all three tests are positive.

The positive and negative predictive values, respectively, are defined correspondingly.

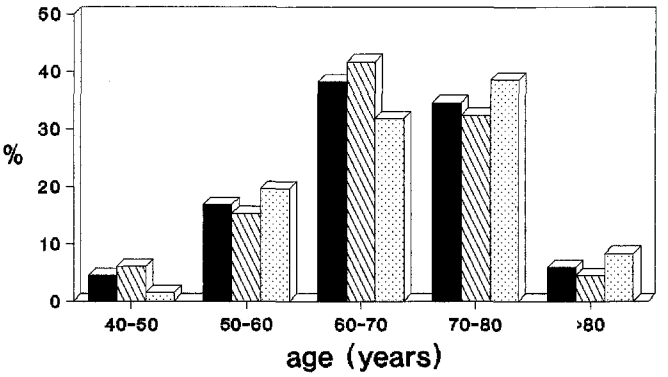

Fig. 1. Distribution of patients' age. ■ Total cohort (376); ▨ non-cancer (244); ⊡ cancer (132)

Results

Figure 1 illustrates the age distribution of the cancer patients, showing one peak in the seventh decade and another in the eighth decade. Remarkable is the finding that as many as one-fifth of the tumor patients were younger than 60 years of age.

Single-modality approach

Table 1 demonstrates the diagnostic characteristics of the modalities employed in the assessment of the different entities. To allow a comparison of the present results with initial reports on PSA in the early 1980s, the normal reference interval of 0–2.7 ng/ml recommended at those times is listed additionally. Statistical analysis of the mean PSA values obtained in the tumorous and non-cancerous patients revealed a highly significant difference between the two cohorts ($P < 0.005$).

Two-modality approach

Using two modalities and connecting the results in an "or" fashion increases the sensitivity of this approach, but a remarkable loss of specificity simultaneously obtained as compared with the characteristics of the modalities used as single measures (Table 2). A positive test result would not justify subsequent invasive diagnostic measures since almost half of the healthy patients would undergo biopsy unnecessarily. However, the combination "DRE or PSA > 4 ng/ml" has to be emphasized because it proved to be superior in sensitivity by 13.7% as compared with the combination "DRE or TRUS."

Table 1. Efficacy of the single modalities in 132 patients with pCa and 244 patients with BPH

Method	PCA-positive	BPH-negative	Sensitivity (%)	Specificity (%)	Positive pred. value (%)	Negative pred. value (%)
DRE	106	170	80.3	69.7	58.9	86.7
TRUS	101	152	76.5	62.3	52.3	83.1
PSA (2.7)	123	94	93.2	38.5	45.1	91.3
PSA (4.0)	116	121	87.9	49.6	48.5	88.3
PSA (10.0)	84	186	63.6	76.2	59.2	79.5

PSA values are expressed in ng/ml. *pCa*, Prostate cancer; *pred. value*, predictive value

Table 2. Efficacy of two modalities as determined using an "or" combination, i.e., only one of the two being indicative of pCa, in 132 patients with pCa and 244 patients with BPH

Method	PCA-positive	BPH-negative	Sensitivity (%)	Specificity (%)	Positive pred. value (%)	Negative pred. value (%)
DRE or TRUS	110	138	83.3	56.6	50.9	86.3
DRE or PSA (2.7)	130	60	98.5	24.6	41.4	96.8
DRE or PSA (4.0)	128	80	97.0	32.8	43.8	95.2
DRE or PSA (10.0)	123	124	93.2	50.8	50.6	93.2
TRUS or PSA (2.7)	130	54	98.5	22.1	40.6	96.4
TRUS or PSA (4.0)	128	72	97.0	29.5	42.7	94.7
TRUS or PSA (10.0)	123	114	93.2	46.7	48.6	92.7

PSA values are expressed in ng/ml. *pCa*, Prostate cancer; *pred. value*, predictive value

Connecting the test results of two modalities in an "and" fashion slightly decreases the sensitivity as compared with the characteristics of the single modalities, but a remarkable increase in specificity is achieved (Table 3). The optimal balance between sensitivity and specificity is accomplished with the combination "DRE and PSA > 4 ng/ml"; malignant transformation is assessed in 71.2% of cases with a specificity of 86.5%. The combination of "DRE and PSA > 10 ng/ml" would allow a further increase in specificity; however, almost one-fifth of all prostate cancers remain undetected as shown by the corresponding sensitivity loss of 20.4%. The combination of "DRE and PSA > 4 ng/ml" is also superior as compared with "TRUS and PSA > 4 ng/ml" in terms of sensitivity and specificity. The approach "DRE and TRUS" as compared with "DRE and PSA > 4 ng/ml" allows a minimal increase of 2.3% in sensitivity but carries a specificity loss of 11.1%. The test combinations in couples demonstrate that TRUS does not provide an additional benefit to DRE or PSA determination.

Three-modality approach

The three-modality approach does not confirm our initial expectations [1] (Table 4). Excluding the combinations with PSA > 2.7 ng/ml, since 4 ng/ml is now the standard normal value, the combination of "DRE and TRUS and PSA > 4 ng/ml" with its specificity of 90.2% seems to be the best. However, the gain in specificity as compared with "DRE and PSA > 4 ng/ml" simultaneously carries a greater sensitivity loss of 6.8%. Applying "DRE or TRUS or PSA > 4 ng/ml" results in the same sensitivity achieved with "DRE or PSA > 4 ng/ml" but is associated with a loss of 5.3% in specificity. The optimal specificity of 96.3% is achieved by "DRE and TRUS and PSA > 10 ng/ml," but only at the cost of a failure to detect more than half of all cancer patients. Also in the triple approach, TRUS does not provide additional information.

Algorithm

Considering the obvious lack of additional information associated with using the diagnostic measures in a triple combination as well as the limited specificity of the single modalities, two approaches deserve closer attention: "DRE *or* PSA > 4 ng/ml" and "DRE *and* PSA > 4 ng/ml." Although the first is marked by a high sensitivity of 97%, the latter exhibits an outstanding specificity of 86.5%, which makes the application of fine needle biopsy reasonable to prove the malignancy histologically in 71.2% of the patients.

The difference in sensitivity of 25.8% between this combination and the value of 97% provided by "DRE or PSA > 4 ng/ml" is created by the subgroup of patients in whom only one marker is indicative of malignancy. Thus, the combination "DRE and PSA > 4 ng/ml" does not seem to be suitable for use as a single screen due to its sensitivity of only 71.2%. Therefore, an additional raster utilizing the indicative potential of the combination "DRE or PSA > 4 ng/ml," which allows a detection rate of 97%, appears suitable. Since the specificity of the lat-

Table 3. Efficacy of two modalities as determined using an "and" combination, i.e., both being suggestive for pCa, in 132 patients with pCa and 244 patients with BPH

Method	PCA-positive	BPH-negative	Sensitivity (%)	Specificity (%)	Positive pred. value (%)	Negative pred. value (%)
DRE and TRUS	97	184	73.5	75.4	61.8	84.0
DRE and PSA (2.7)	99	204	75.0	83.6	71.2	86.1
DRE and PSA (4.0)	94	211	71.2	86.5	74.0	84.7
DRE and PSA (10.0)	67	232	50.8	95.1	84.8	78.1
TRUS and PSA (2.7)	94	192	71.2	78.7	64.4	83.5
TRUS and PSA (4.0)	89	201	67.4	82.4	67.4	82.4
TRUS and PSA (10.0)	62	224	47.0	91.8	75.6	76.2

PSA values are expressed in ng/ml. *pCa*, Prostate cancer; *pred. value*, predictive value

Table 4. Efficacy of three modalities as determined using an "or" and "and" combination, i.e., one of the three or all three being suggestive for pCa, in 132 patients with pCa and 244 patients with BPH

Method	PCA-positive	BPH-negative	Sensitivity (%)	Specificity (%)	Positive pred. value (%)	Negative pred. value (%)
DRE or TRUS or PSA (2.7)	130	49	98.5	20.1	40.0	96.1
DRE or TRUS or PSA (4.0)	128	67	97.0	27.5	42.0	94.4
DRE or TRUS or PSA (10.0)	124	103	93.9	42.2	46.8	92.8
DRE and TRUS and PSA (2.7)	90	213	68.2	87.3	74.4	83.5
DRE and TRUS and PSA (4.0)	85	220	64.4	90.2	78.0	82.4
DRE and TRUS and PSA (10.0)	59	235	44.7	96.3	86.8	76.3

PSA values are expressed in ng/ml. *pCa*, Prostate cancer; *pred. value*, predictive value

Table 5. Suggested algorithm for the early detection of prostate cancer

DRE+ and PSA	>4 ng/ml → biopsy
DRE+ or PSA	>4 ng/ml → 3-monthly control
DRE− and PSA	>4 ng/ml → yearly preventive check-up

ter combination (32.8%) would not justify invasive diagnostic procedures, in this group of patients with only one parameter suspicious for prostate cancer, a short-term control appears more appropriate (Table 5).

In this context, it is emphasized that the percentage of change in PSA levels per year was found to be significantly greater in men with prostate cancer as compared with men with BPH ($P<0.03$). These data suggest that serial determinations of PSA levels may be useful in detecting prostate cancer earlier [2].

If both parameters are negative, e.g., the DRE is normal and PSA levels are <4 ng/ml, there is a probability of 95.2% that the patient will not suffer from prostate cancer. In these low-risk cases, check-ups at longer intervals seem to be acceptable.

The use of such an approach according to the corresponding probability of selection would allow the detection of 71.2% of all prostate cancer patients and would provide the histologic proof as early as at their first presentation. In addition, 25.8% of the tumorous patients could be detected by subsequent short-term controls. Only 3% of tumorous cases are not diagnosed by this strategy (Table 6). Whereas 32.8% of the non cancerous patients are correctly diagnosed, 13.5% would undergo biopsy and 53.7% would be subjected to further control check-ups unnecessarily. However, the latter seems tolerable, since DRE and blood tests are noninvasive diagnostic measures.

Discussion

The study of the American College of Surgeons [14] reports 5-year survival values for patients with prostate cancer according to the clinical stages A, B, C, and D of 85%, 77%, 65.5%, and 30%, respectively. Paulson et al. [11] found a 5-year survival value of 90% for patients with stages T1b and T2 disease after radical prostatectomy. Approximately 85% of patients with lymphatic spread of prostatic carcinoma develop distant metastases within 5 years, and the vast majority of these die within 3 years thereafter. Of patients with stage D2 disease, about 50% die of prostate cancer within 30 months, 80% die within 5 years, and 90% succumb within 10 years [3]. These data underscore the possibility of a cure in cases of a diagnosis at an early stage, when the disease is confined to the gland, and simultaneously define the requirements for an adequate diagnostic approach.

Table 6. Probabilility of selection in checking a population for prostate cancer according to the algorithm

pCa Patients:			
True positive	→	histologic confirmation	71.2%
Control	→	postponed detection	25.8%
False negative	→	loss	3.0%
Total			100.0%
Non-pCa patients:			
False positive	→	biopsy unnecessary	13.5%
		control unnecessary	53.7%
True negative	→		32.8%
Total			100.0%

Using DRE as the "gold standard," 32% of carcinomas will be missed, even by experienced examiners [9]. Thompson et al. [15] presented the results of routine urologic screening of 2005 men between 40 and 70 years old and found DRE to be an insensitive screening device with poor predictive value. As reasons for the insensitivity, the authors discussed the localization of the tumor as well as the missing palpable abnormality and suggested as early as in 1984 the use of adjunctive tools for the detection of adenocarcinoma of the prostate [15]. In our study we obtained similar results. Exclusive performance of DRE had not detected 20% of cancers; in addition, the specificity of the test with only 69.7% due to a variety of benign reasons for induration cannot be considered adequate.

The sensitivity of TRUS (76.5%) proved to be inferior as compared with DRE, as did its specificity and disappointing positive predictive value of 52.3%. Even though we used the most advanced technology by employing a 7.5-MHz multifocal multiplane transducer, we obtained an improvement of only 20% in the results reported by Chodak et al. [5].

Statistical analysis of the PSA data at first confirmed this glycoprotein to be a tumor marker due to the highly significant difference between cancerous and noncancerous patients. Furthermore, our results substantiate the extension of the normal reference interval from 0–2.7 ng/ml in the early 1980s to the currently worldwide accepted range of 0–3.9 ng/ml as recommended by the manufacturer. The actual normal range demonstrates a loss of 5.3% in sensitivity; however, the specificity is simultaneously increased by 11.1%. A further extension up to 9.9 ng/ml proved to be inappropriate in discriminating these entities, because 24.3% of the cancer patients in our study would not have been detected.

In our cancer patients PSA levels were found to be above the normal range in 87.9% of cases, but this also applied to 50.4% of the BPH patients. Due to its organ-specific but not tumor-specific character, PSA is not suitable as a single measure for early detection of prostate cancer as demonstrated by its specificity of 49.6%.

It is noteworthy that the sensitivity, specificity, and predictive value requirements of a test differ in different settings [12]. In an early detection program the specificity has to be reasonably high. Even though the patients investigated represent a selected group since they were recruited in the setting of a urology department, the statements regarding the quality of the single measures for the detection of prostate cancer are not affected adversely. Considering the specificity of the single tests, it becomes obvious that none meets the requirements for an early detection program. Combining DRE with TRUS in an "or" fashion achieves an increase of only 2% in sensitivity as

compared with DRE alone. In contrast, the combination of DRE and PSA > 4 ng/ml in an "or" fashion provides a sensitivity increase of 16.7%. However, this screen is hampered by its low specificity of 32.8% and is not appropriate as a single measure for an early detection program. As an improved first raster, the combination "DRE and PSA > 4 ng/ml" recommends itself, meeting the outlined conditions regarding specificity while simultaneously exhibiting an acceptable sensitivity.

When all possible combinations of the modalities in "or" and "and" connections are considered, the variability of prostate cancer with respect to its clinical, immunoserologic, and sonographic phenotype becomes apparent. This heterogeneity is furthermore reflected by the observation that in the search for an optimal approach for early detection, a gain of specificity is accompanied by a loss of sensitivity, and vice versa. Our data confirm the results of Catalona et al. [4] that the combination of the serum PSA concentration and DRE increases the rate of detection of prostate cancer. However, we could not prove that any additional information was provided by TRUS. Using palpation and TRUS (7.0 MHz axial, 5.0 MHz sagittal) in a study of 315 asymptomatic men, Palken et al. [10] also found both methods equieffective and recommended the clinical investigation with respect to costs.

Our work exclusively demonstrates the superiority of a combined approach over the "gold standard" in the early detection of prostate cancer. By no means does this study provide information about the value of an early detection program with regard to the morbidity and mortality of prostate cancer. This question can be answered only by a prospective multicenter randomized study that is based on the algorithm outlined herein and includes treatment modalities and patient care as well. Meanwhile, opportunities to detect prostate cancer early should not be missed by the urologic community employing the knowledge gained thus far about the characteristics of various diagnostic measures.

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